Tetrahedron Letters,Vol.25,No.32,pp 3467-3470,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

A CONVENIENT FAMILY OF CHIRAL SHIFT REAGENTS FOR MEASUREMENT OF ENANTIOMERIC EXCESSES OF SULFOXIDES

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Abstract

(R)(-)-N-(3,5-dinitrobenzoyl)-α-phenylethylamine is a good chiral shift reagent for sulfoxides such as Ar-(SO)-CH_3 (Ar=substituted phenyl,naphthyl) or R-(SO)-CH_3 (R=t-Bu,Cyclohexyl,n-Octyl). 1-Naphthyl propyl sulfoxide was also successfully resolved. The sharpness of the signals allows to measure e.e.'s in the range of 90%. Twenty-five examples are given.

Chiral sulfoxides are taken increasing importance in organic synthesis[1-3]. However,in many cases the maximum specific rotation of these compounds is unknown. Chromatographic methods using chiral phases are efficient[4,5],but they usually need an aromatic group as part of the sulfoxide structure.Optically active solvents[6] or lanthanide chiral shift reagents are very useful in nmr analysis,particularly Eu(hfc)$_3$ where hfc stands for (n-heptafluoropropyl)hydroxymethylene-d-camphorato[7-9].This reagent applies to various kinds of sulfoxides but there is often peak broadening and incomplete separation and it is difficult to accurately measure high enantiomeric excesses (∿90% e.e.).Recently,we discover an efficient method of asymmetric oxidation of sulfides of wide applicability[10],and we were faced to measure e.e. of various sulfoxides,many of them not previously resolved.We found that (R)-(-)-N-(3,5-dinitrobenzoyl)-α-phenylethylamine 1 acts a chiral shift reagent in nmr when used in $CDCl_3$ or CCl_4.

Both enantiomers of the reagent are easily obtained from commercially available starting material,(R) or (S)-α-phenylethylamine.Thus (+)-1-phenylethylamine (Fluka) is quantitatively acylated by 3,5-dinitrobenzoylchloride in $CHCl_3$ in presence of pyridine and 1 is obtained in 90% yield, ($[\alpha]_D^{20}$ = - 17.5° (0.9,acetone),mp = 158-160°C) after a filtration (ether) on neutral alumina.When the commercial starting material is not optically pure it is necessary to recrystallize the product till constant specific rotation.

(R)-2a ($[\alpha]_D^{20}$ = + 9.2° (2,EtOH),mp = 228°C) was also prepared,as well as the amides 2b,2c and $C_6H_5CH(CH_3)NHCOR$ (R=CH_3,CF_3)[11].

Preliminary essays using racemic methyl phenyl sulfoxide (0.15 M) and 2 equivalents of 2 in $CDCl_3$ show in ^1H nmr (100 MHz) a non equivalence of the methyl sulfinyl groups.The peak separations expressed in Hz) are 1.5,2.3,3.2 for 2b,2c and 2a respectively with the clear advantage of an almost no enlargement of the peaks compared with the one observed when europium complexes are used.

We selected the amides with the dinitrophenyl moiety as the best for the chiral shift reagents.We found that 1 is easier to use than the naphthyl analogs 2 because of its better solubility. 1 gives satisfactory results in $CDCl_3$ using one molar equivalent amount per equivalent of sulfoxide.If it is necessary to increase the peak separation,more reagent can be further added (see note h in Ta-

ble 1).The standard conditions for enantiomer analysis are the following : the sulfoxide is dissolved in $CDCl_3$ (0.10-0.30 M) ,ne equivalent of reagent is added and ^1H nmr is recorded.Some results are listed in Table 1.Examples of spectra are indicated in figures 1-4.

The method tolerates many functional groups and applies very well to various kinds of methyl sulfoxides.The only cases with no peak separation were methyl-4-pyridyl sulfoxide and p-(CO_2Et)phenyl methyl sulfoxide.The methyl group is useful but not indispensable,thus 2-naphthyl-n-propyl sulfoxide could be analyzed by separation of the proton at C_1 on the naphthalene ring.Whenpossible it is better to use CCl_4 as solvent,thus racemic methyl p-tolyl sulfoxide and (+)-2c (1:1) gave a methyl peak separation at 100 MHz of 2.3 Hz in $CDCl_3$ and of 5.4 Hz in CCl_4.No separation was obtained in CD_3CN.

$Eu(hfc)_3$ gave poor peak separation for many of the sulfoxides tried,especially in the cases with high e.e. where accurate measurements were difficult.In some cases (methyl-4-nitrophenyl sulfoxide,methyl-4-pyridyl sulfoxide,methyl-2-pyridyl sulfoxide,..) no separation at all was observed with $Eu(hfc)_3$ because of the enlargement of the peaks[12].

The origin of the non equivalence between sulfoxide enantiomers with 1 or 2 presumably lies in the formation of complexes because of hydrogen bonds between the sulfinyl and the NH groups.Charge transfer could also operate to some extent[13].

In conclusion,1 is a simple and inexpensive chiral shift reagent for routine enantiomeric analysis of many sulfoxides[14].

Acknowledgments

We thank CNRS for its financial support.

References and Notes

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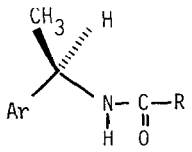
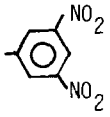
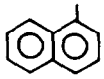
(11) No interference of the reagents 1 or 2 with the absorption of the methyl sulfinyl group is observed in nmr.
(12) $Eu(hfc)_3$ (Aldrich) was used as received.
(13) For aromatic sulfoxides the chiral recognition model could be similar to the one proposed for HPLC enantiomers separation where the chiral phase is based on the N-3,5-dinitrobenzoylphenyl glycine moiety[5].
(14) A preliminary screening was undertaken with other families of substrates able to bind by hydrogen bond. Nmr spectra of racemic 2-octanol or 2-methylcyclohexanone were not resolved by addition of 1.It was found that racemic $CH_3CH(N_3)CON(CH_3)_2$ gives in CCl_4 four signals for N-methyl groups and two doublets for CH_3-CH. The non equivalencies (at 100 MHz) are respectively of 9 Hz and 2.5 Hz when two equivalents of 1 are used.The same shift reagent also differentiates the two antipodes of racemic N-acetyl-α-phenylethylamine ($\Delta\delta$ = 11.3 Hz on $CH_3(CH)$).



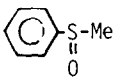
1 Ar =  R = 

2a Ar =  R = "

2b Ar = " R = $-CH_3$

2c Ar = " R = $-CF_3$

Figure 1



racemic

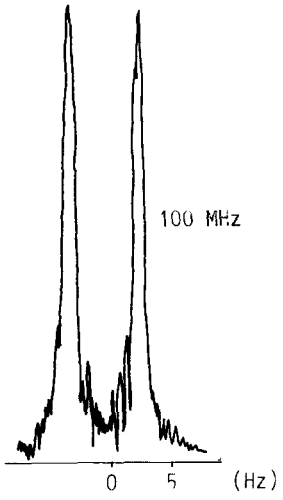
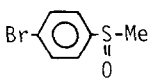


Figure 2



racemic

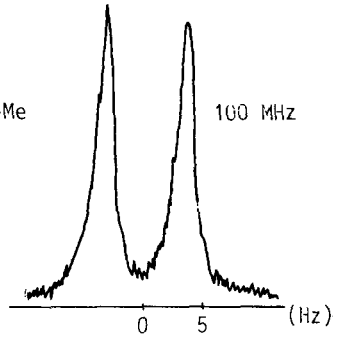


Figure 3

$CH_3(CH_2)_7$-S-CH_3
O

77% e.e.

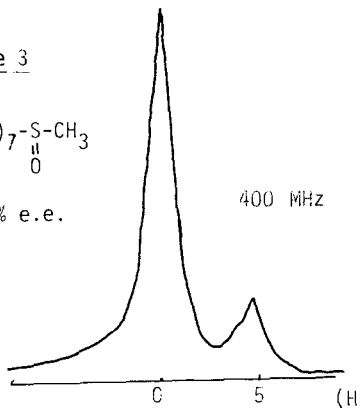
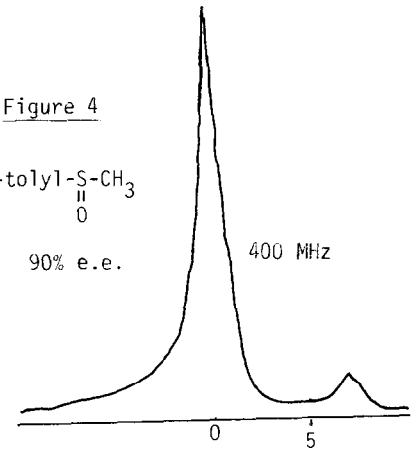


Figure 4

p-tolyl-S-CH_3
O

90% e.e.



Figures : ^{1}H nmr of R-S-Me (O) group in the presence of :

Figure 1 : 2.0 equivalents of 2c in CCl_4
Figure 2 : 1.6 equivalents of 2c in CCl_4
Figure 3 : 1.0 equivalent of 1 in $CDCl_3$
Figure 4 : 1.0 equivalent of 1 in $CDCl_3$

TABLE 1

Enantiomeric excesses of sulfoxides R_1-(SO)-R_2 measured by ^1H nmr, with 1 or 2 as chiral shift reagents[a].

R_1	R_2	Chiral reagent	$\Delta\delta$(Hz)[c]	$\Delta_{1/2}$ (H_z)[c]	$(\alpha)_D$(acetone)	e.e. (%)
p-tolyl	Me	1[b]	6.5	1.3	+ 131°	90
p-nitrophenyl	Me	1[b]	4.4	1.6	+ 77.1°	77
p-CH_2OH phenyl	Me	1[b]	5.7	1.3	+ 77°	76
p-OH phenyl	Me	1[b]	8.1	1.8	+ 45°	50
2-pyridyl	Me	1[b]	9.5[e]	5.5	+ 34°	57
n-C_8H_{17}	Me	1[b]	4.4	1.4	- 44°	71
t-Bu	Me	1[b]	5.3	1.0	- 15°	53
c-C_6H_{12}	Me	1[b]	5.2	2.6	- 44.5°	54
$Ph(CH_2)_3$	Me	1[b]	4.4	1.4	- 29°	50
2-$C_{10}H_7$	Me	1[b]	4.7[d]	1.6	+ 120°	85
2-$C_{10}H_7$	Me	1[b]	10.0	1.8	+ 127°	90
2-$C_{10}H_7$	n-Pr	1[b]	5.7	4.4	+ 40°	24
p-tolyl	Me	1[i,j]	5.0	1.3	+ 128°	88
p-tolyl	Me	1[k]	7.0	1.3	+ 128°	88
phenyl	Me	2a[f,h]	3.2	-	0	0
"	Me	2b[f,h]	1.5	-	0	0
"	Me	2c[f,h]	2.3	-	0	0
"	Me	2c[g]	7.7	-	0	0
p-tolyl	Me	2c[f]	2.3	-	0	0
"	Me	2c[g]	5.4	-	0	0
p-bromophenyl	Me	2a[g]	2.4	-	0	0
"	Me	2c[g,i]	6.1	-	0	0
benzyl	Me	2c[g,i]	4.6	-	0	0
ethyl	Me	2c[g]	5.7	-	0	0
n-propyl	Me	2c[g,i]	6	-	0	0

a) One mol equivalent unless stated.

b) Measurement at 400MHz in $CDCl_3$, $[R_1$-(SO)-$R_2]$ = 0.10-0.30 M.

c) $\Delta\delta$(Hz) is the separation between the signals of two enantiomers. The major peak is at lower field. $\Delta_{1/2}$(Hz) is the width at half height for the signal of the major enantiomer.

d) 0.5 mol equivalent of reagent

e) In $CDCl_3$ + 10% CCl_4

f) Measurement at 100MHz in $CDCl_3$

g) Measurement at 100MHz in CCl_4

h) 2 mol equivalent of reagent

i) 1.6 mol equivalent of reagent

j) Measurement at 250MHz in $CDCl_3$

k) Measurement at 250MHz in CCl_4

(Received in France 23 April 1984)