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Highly Diastereoselective Reduction of Chiral β-Imino Sulfoxides to the Corresponding β-Amino Sulfoxides

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ABSTRACT: The hydride reduction of chiral β-imino sulfoxides with 1-benzyl-1-azonia-4-azabicyclo[2, 2, 2]octane tetrahydroborate (BAAOTB) to the corresponding β-amino sulfoxides is described. © 1997 Elsevier Science Ltd.

β-Amino sulfoxides are useful compounds for the asymmetric synthesis of chiral alkaloids.[1-3]

As an extension of our work in this area we have embarked on a project aimed at asymmetric reduction of β-enamino sulfoxides. Chiral β-imino sulfoxides, cyclic imino sulfoxides and β-keto sulfoxides have been reduced with $LiAlH_4$, $NaBH_4$ and DiBAL.[4, 5, 6] In our hands the reduction of β-imino sulfoxides with these reagents gave the corresponding β-amino sulfoxides with poor diastereoselectivity (<64:36).[7]

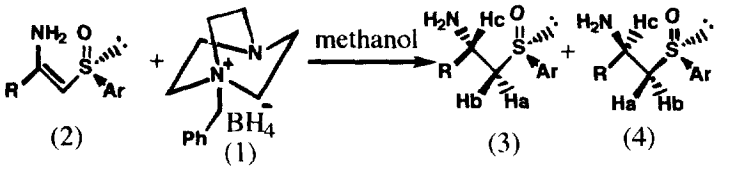
RESULTS AND DISCUSSION

We decided to prepare β-amino sulfoxides (3) and (4) via a diastereoselective reduction of the β-imino sulfoxides (2).[7, 8] We anticipated that reduction of compound (2) with BAAOTB (1)[9] due to steric hindrance of the reducing reagent may be more diastereoselective.

We now describe the diastereoselective reduction of compound (2) with reducing reagent (1) in methanol. Addition of 1-benzyl- 1-azonia-4-azabicyclo[2, 2, 2]octane tetrahydroborate(BAAOTB) (1) to β-imino sulfoxides (2) gave the β-amino sulfoxides (3) and (4) in 80-93% yield and diastereoselection (80:20-98:2) (Scheme 1, Table 1).

The ^1H NMR spectrum of both diastereoisomers (3c) and (4c) are clearly evident as a doublet of doublets at δ 3.34 (dd, J=6.7 and 13.4 Hz) respectively. Integration of these signals indicated that the diastereoisomeric ratio was 92:8. The product diastereoselection increased as the steric demands of the R substituent of the β-enamino sulfoxides increased (Table 1, entries 5 and 10). The highest product diastereoselection was obtained with β-enamino sulfoxide (2j) as shown in Table 1.

Scheme 1.



(2) (1) (3) (4)

a: Ar=Ph R=Me b: Ar=Ph R=3,4-dimethoxyphenyl c: Ar=Ph R=Ph

d: Ar=Ph R=$PhCH_2$ e: Ar=Ph R=*t*-Bu f: Ar=Tol R=Me

g: Ar=Tol R=3,4-dimethoxyphenyl h: Ar=Tol R=Ph

i: Ar=Ar=Tol R=$PhCH_2$ J: Ar=Tol R=*t*-Bu

Table 1: Reduction of β-enamino sulfoxide (2) to β-amino sulfoxides (3) and (4) .

entry	compound (2)	Reaction Time (min.)	yield (%) (3)+(4)	d.r. (3):(4)
1	(2a)	120	93	80:20
2	(2b)	130	90	85:15
3	(2c)	100	93	90:10
4	(2d)	120	90	85:15
5	(2e)	150	80	95:5
6	(2f)	120	90	85:20
7	(2g)	140	85	85:15
8	(2h)	100	90	95:5
9	(2i)	120	90	93:7
10	(2j)	150	80	98:2

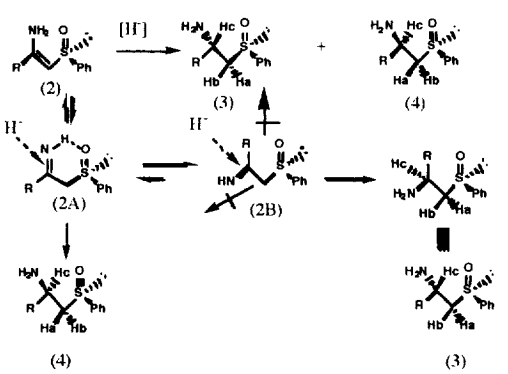
The relative (1*S**,*Rs**) stereochemistry was assigned to the major diastereomeric products (3) based on the similarity of their ^{1}H NMR spectra to those of compounds that were obtained from the addition of lithiated methyl phenyl sulfoxide to oxaziridines and nitrones .[1-3, 6b] The ^{1}H NMR spectral data for compounds (3a-j) and (4a-j) are summarised in Table 2. In each case H_c for the major diastereoisomer (3) shifts downfield as shown in Table 2. The J_{ac} and J_{bc} values are also consistent with these compounds having the relative (1*S**,*Rs**) stereochemistry.

Table 2. ^{1}H NMR ($CDCl_3$) chemical shifts and coupling constants (Hz) for compounds (3a-j).

Compound	chemical shifts (ppm)			coupling constants (Hz)		
	H_a	H_b	H_c	J_{ac}	J_{bc}	J_{ab}
(3a)	2.99	2.76	3.99	10.2	3.2	13.6
(3b)	3.28	3.14	5.18	10.8	4.8	13.6
(3c)	3.23	3.12	5.22	10.0	4.4	13.2
(3d)	3.39	3.32	4.36	8.4	5.2	13.6
(3e)	3.58	2.94	4.55	11.0	4.0	13.2
(3f)	3.00	2.93	4.00	10.2	3.4	13.4
(3g)	3.91	3.40	5.28	10.8	3.8	13.6
(3h)	3.16	3.06	5.28	10.0	3.6	13.7
(3i)	3.51	3.40	4.46	10.4	4.8	13.6
(3j)	3.58	2.94	4.32	11.0	4.6	13.4

In the reduction of (2), the addition of BAAOTB (1) was thought to occur by attack of hydride on the imine forms (2A) and (2B) via the conformations shown in Scheme 2. Conformation (2A) is internally H-bonded while conformation (2B) is the one in which dipole-dipole interactions between the C=NH and the S=O groups are minimized. Addition should occur from the less hindered face of the imine double bond, that is the face that is *anti* to the S-Ph in (2A) and (2B) to give (3) and (4) respectively. At room temperature there is a high preference for attack on conformation (2B), giving product (3) as the major diastereomeric product.

Scheme 2. Reduction of β-imino sulfoxide (2) to β-amino sulfoxide (3) and (4).



In conclusion we have discovered a new and useful method for preparing β-amino sulfoxides in high diastereomeric purity based on the reduction of β-imino sulfoxides with 1-benzyl-1-azonia-4-azabicyclo[2, 2, 2]octane tetrahydroborate(1) as the selective and mild reducing reagent.

Experimental

The 1-benzyl-1-azonia-4-azabicyclo[2, 2, 2]octane tetrahydroborate(BAAOTB) (1) was prepared from 1-benzyl-1-azonia-4-azabicyclo[2, 2, 2]octane by the known method.[9] All ^1H NMR and ^{13}C spectra were recorded at 400 MHz in $CDCl_3$ solution.

Reduction of (2) to β-amino sulfoxides (3) and (4).

General procedure:

To 2 mmol of β-imino sulfoxide (2)[7] in methanol (20 mL) was added BAAOTB (2 mmol, 0.44 g) in small portions over 15 min. at room temperature. The reaction was stirred until TLC showed complete disappearance of starting material, which required 100-150 min. depending on the substrate, and then the methanol was evaporated under reduced pressure. Water (50 mL) was then added to the residue which was extracted with dichloromethane (2x25 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvent, and chromatographic purification (silica gel, hexane/ethyl acetate 8:2) gave a mixture of (3) and (4) (Table 1).

(R^*_S,1S*)-1-Phenylsulfinyl-2-propylamine (3a).

Oil. IR (film) 3600-3200(br), 3300 (sharp), 1035 cm^{-1}. ^1H NMR δ 7.52 -7.27(m, 5H), 3.99 (m, J =3.2, 10.2 Hz, 1H), 2.99 (dd, J = 10.2, 13.6 Hz, 1H), 2.76 (dd, J = 3.2, 13.6 Hz, 1H), 1.42 (d, 3 H, CH_3). ^{13}C NMR δ 141.2, 140.9, 140.6, 129.6, 128.3, 127.2, 126.6, 123.6, 65.0, 59.1, 33.8. MS (CI) m/z 183 (100, M^+). Anal calcd for $C_9H_{13}NOS$: C, 58.99; H, 7.16; N, 7.65 %. Found: C, 58.86; H, 7.11; N, 7.59 %.

(R^*_S,1R*)-1-phenylsulfinyl-2-propylamine (4a).

^1H NMR (in part) δ 3.88. (m, J = 6.6, 9.6 Hz, 1H); 3.08 (dd, J = 6.6, 13.2 Hz, 1H), 1.16 (d, 3 H, CH_3).

(R^*_S,1S*)-2-Phenylsulfinyl-1-(3,4-dimethoxyphenyl)-2-ethylamine (3b)

Oil. ^{1}H NMR δ 7.88-6.68 (m, 8 H), 5.18(dd, J=4.8, 10.8 Hz,1H), 3.95 (s, 3H, OMe), 3.91 (s, 3 H. OMe), 3.28 (dd, J=10.8, 13.6 Hz, 1 H) 3.14 (dd, J=4.8, 13.6 Hz, 1 H). MS, m/z, 305 (100 %, M^+). Anal calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.28; N, 4.59 %. Found: C, 62.99; H, 6.34; N, 4.48 %.

(R^*_S,1R^*)-2-Phenylsulfinyl-1-(3,4-dimethoxyphenyl)-2-ethylamine (4b)

^{1}H NMR (in part) δ 5.03 (dd, J=6.8, 8.6 Hz, 1H), 3.38 (dd, J=8.6, 13.2 Hz, 1H), 3.08 (dd, J=6.8, 13.2 Hz, 1H).

(R^*_S,1S^*)-2-Phenylsulfinyl-1-(phenyl)-2-ethylamine (3c)

Oil. ^{1}H NMR δ 7.88-6.76 (m, 10 H), 5.22 (dd, J= 4.4, 10.0 Hz, 1H), 3.23 (dd, J=10.0, 13.2 Hz, 1 H), 3.12 (dd, J= 4.4, 13.2 Hz, 1 H). MS m/z, 245 (100 %, M^+). Anal calcd. for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71 %. Found: C, 68.51; H, 6.13; N, 5.67 %.

(R^*_S,1R^*)-2-Phenylsulfinyl-1-(phenyl)-2-ethylamine (4c)

^{1}H NMR (in part) δ 5.14 (dd, J=6.7, 8.2 Hz, 1H), 3.34 (dd, J=8.2, 13.4 Hz, 1H), 2.98 (dd, J=6.7, 13.4, 1H).

(R^*_S,1S^*)-2-Phenylsulfinyl-1-(benzyl)-2-ethylamine (3d).

M.p. 150-151 °C. IR (nujol), 3509, 3330, 2950, 1030cm^{-1}. ^{1}H NMR δ 7.2-7.8 (m, 10H) 4.36 (dd, J = 5.2, 8.4 Hz, 1H), 3.84 (d, J = 13.6 Hz, 1H), 3.68 (d, J = 13.6 Hz, 1H), 3.39 (dd, J = 5.2, 13.6 Hz, 1H), 3.32 (dd, J = 8.4, 13.6 Hz, 1H). MS(CI) m/z 260 ($M+H^+$, 20), 260 (75), 230 (50), 211 (100), 197 (60), 142 (100), 127 (100), 106 (80). Anal calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.4%. Found: C, 70.08; H, 6.59; N, 5.32%.

(R^*_S,1R^*)-2-Phenylsulfinyl-1-(benzyl)-2-ethylamine (4d).

^{1}H NMR (in part) δ 4.26 (dd, J = 6.4, 10.4 Hz, 1H), 3.06 (dd, J = 6.4, 13.6 Hz, 1H).

(R^*_S,1S^*)-2-Phenylsulfinyl-1-(*tert*-butyl)-2-ethylamine (3e).

M.p. 124-125 °C: IR (nujol) 3520, 3330, 1030 cm^{-1}. ^1H NMR δ 8.2 (m, 1H), 7.2-7.8 (m, 4H), 4.55 (dd, J = 4.0, 11 Hz, 1H), 3.58 (dd, J = 11, 13.2 Hz, 1H), 2.94 (dd, J = 4.0, 13.2 Hz, 1H), 0.981 (s, 9H). ^{13}C NMR δ 144.6, 130.5, 129.5, 128.5, 127.3, 126.9, 126, 125, 69.3, 63.7, 28.8, 26.8. MS(CI) m/z 226 (75, $M+H^+$), 262 (25). Anal calcd for $C_{12}H_{19}NOS$: C, 63.96; H, 8.5; N, 6.22%. Found: C, 64.1; H, 8.4; N, 6.34%.

(R^*_S,1R^*)-2-Phenylsulfinyl-1-(*tert*-butyl)-2-ethylamine (4e).

^1H NMR (in part) δ 3.64 (dd, J = 10.8, 13.6 Hz, 1H), 3.01 (dd, J = 6.4, 13.6 Hz, 1H), 1.02 (s, 9H).

(R^*_S,1S*)-1-*p*-tolylsulfinyl-2-propylamine (3f).

Oil. IR (film) 3600-3200(br), 3300 (sharp), 1035 cm^{-1}. ^1H NMR δ 7.52 (d, J=8.2 Hz, 2H), 7.27(d, J=8.2 Hz 2H), 4.06 (m, J =3.4, 10.2 Hz, 1H), 3.00 (dd, J = 10.2, 13.4 Hz, 1H), 2.93 (dd, J = 3.4, 13.4 Hz, 1H), 2.39 (s, 3H), 1.42 (d, 3 H, CH_3). ^{13}C NMR δ 141.2, 140.9, 140.6, 129.6, 128.3, 127.2, 126.6, 123.6, 65.0, 59.1, 33.8., 20.9. MS (CI) m/z 197 (100, M^+). Anal calcd for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10 %. Found: C, 60.81; H, 7.74; N, 7.06 %.

(R^*_S,1R^*)-1-*p*-tolylsulfinyl-2-propylamine (4f).

^1H NMR (in part) δ 3.32. (m, J = 8.4, 13.1 Hz, 1H); 2.81 (dd, J = 5.5, 13.1 Hz, 1H), 1.16 (d, 3 H, CH_3).

(R^*_S,1S*)-2-*p*-tolylsulfinyl-1-(3,4-dimethoxyphenyl)-2-ethylamine (3g)

m.p 200-201. ^1H NMR δ 7.88-6.68 (m, 7 H), 5.28(dd, J=3.8, 10.8 Hz,1H), 3.95 (s, 3H, OMe), 3.91 (s, 3 H, OMe), 3.40 (dd, J=10.8, 13.6 Hz, 1 H) 3.28 (dd, J=3.8, 13.6 Hz, 1 H), 2.41 (s, 3H). MS, m/z, 319 (100 %, M^+). Anal calcd. for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39 %. Found: C, 63.851; H, 6.73; N, 4.37 %.

(R^*_S,1R^*)-2-*p*-tolylsulfinyl-1-(3,4-dimethoxyphenyl)-2-ethylamine (4g)

^1H NMR (in part) δ 5.23 (dd, J=4.8, 9.6 Hz, 1H), 3.58 (dd, J=9.6, 13.6 Hz, 1H), 3.09 (dd, J=4.8, 13.6 Hz, 1H).

(R^*_S,1S*)-2-*p*-tolylsulfinyl-1-(phenyl)-2-ethylamine (3h)

m.p 198-200. ^{1}H NMR δ 7.49 (d, J=8.2 Hz, 2H), 7.3 (m, 7 H), 5.28 (dd, J= 3.6, 10.0 Hz, 1H), 3.16 (dd, J=10.0, 13.7 Hz, 1 H), 3.06 (dd, J= 3.6, 13.7 Hz, 1 H), 2.39 (s, 3H). ^{13}C NMR 146.6, 141.7, 130.1, 127.66, 124,1, 114.0, 64.1, 54.8, 21.4. MS m/z, 259 (100 %, M^+). Anal calcd. for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40 %. Found: C, 69.58; H, 6.73; N, 5.27 %.

(R^*_S,1R*)-2-*p*-tolylsulfinyl-1-(phenyl)-2-ethylamine (4h)

^{1}H NMR (in part) δ 5.14 (dd, J=4.7, 10.2 Hz, 1H), 3.24 (dd, J=10.2, 13.4 Hz, 1H), 2.98 (dd, J=4.7, 13.4, 1H), 2.32 (s, 3H).

(R^*_S,1S*)-2-*p*-tolylsulfinyl-1-(benzyl)-2-ethylamine (3i).

M.p. 159-161 °C. IR (nujol), 3509, 3330, 2950, 1030cm^{-1}. ^{1}H NMR δ 7.2 (d, J=8.4, 2H), 7.8 (m, 7H) 4.46 (dd, J = 4.8, 10.4 Hz, 1H), 3.89 (d, J = 13.2 Hz, 1H), 3.79 (d, J = 13.6 Hz, 1H), 3.51 (dd, J = 4.8, 13.6 Hz, 1H), 3.40 (dd, J = 10.4, 13.6 Hz, 1H), 2.34 (s, 3H). MS(CI) m/z 274 ($M+H^+$, 20), 260 (75), 230 (50), 211 (100), 197 (60), 142 (100), 127 (100), 106 (80). Anal calcd for $C_{16}H_{19}NOS$: C, 70.29; H, 7.00; N, 5.12%. Found: C, 70.18; H, 7.19; N, 5.23%.

(R^*_S,1R*)-2-*p*-tolylsulfinyl-1-(benzyl)-2-ethylamine (4i).

^{1}H NMR (in part) δ 4.38 (dd, J = 5.4, 10.4 Hz, 1H), 3.36 (dd, J = 5.4, 13.6 Hz, 1H).

(R^*_S,1S*)-2-*p*-tolylsulfinyl-1-(*tert*-butyl)-2-ethylamine (3j).

M.p. 128-129 °C: IR (nujol) 3520, 3330, 1030 cm^{-1}. ^{1}H NMR δ 7.8 (d, J=8.4, 2H), 7.3-(d, J=8.4, 2H), 4.32 (dd, J = 4.6, 11 Hz, 1H), 3.58 (dd, J = 11, 13.2 Hz, 1H), 2.94 (dd, J = 4.6, 13.2 Hz, 1H), 2.34 (s, 3H), 0.981 (s, 9H). ^{13}C NMR δ 144.6, 130.5, 129.5, 128.5, 127.3, 126.9, 126, 125, 69.3, 63.7, 28.8, 26.8, 24.8. MS(CI) m/z 240 (75, $M+H^+$), 262 (25). Anal calcd for $C_{13}H_{21}NOS$: C, 65.23; H, 8.84; N, 5.85%. Found: C, 65.12; H, 8.92; N, 5.64%.

(R^*_S,1R*)-2-*p*-tolylsulfinyl-1-(*tert*-butyl)-2-ethylamine (4j).

^{1}H NMR (in part) δ 3.41 (dd, J = 10.8, 13.6 Hz, 1H), 2.85 (dd, J = 6.4, 13.6 Hz, 1H), 1.02 (s, 9H).

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REFERENCES:

1 Hajipour, A. R.;. *Synth. Commun.* **1996**, 26, 3627.

2. Hajipour, A. R. *Indian J. Chem.*. **1997**, 36B, 329.

3. Pyne,S. G.; Hajipour, A.R.*Tetrahedron*, **1992,** 48, 9385 .

4. Solladie, G.; Demailly, G.; Greck, C. *J. Org. Chem.* ,**1985**, 50, 1552.

5. Ruano, J. L. G.; Lorente, A.; Rodriguez, J. H. *Tetrahedron Lett.*, 1992, 33, 5637.

6. (a) Carreno, M. C.; Dominguez, E.; Ruano, J. L. G.; Pedregal, C.; Rodriguez, J. H. *Tetrahedron* **1991**, 47, 10035. (b) Pyne, S. G.; Hajipour, A. R., *Tetrahedron*, **1994**, 50, 13501.

7. Hajipour, A. R; Pyne, S. G. unpublished results.

8. Page, P. C. B.; Neil, M. B. V.; Westwood, D. *J. Chem. Perkin Trans.* I, **1988**, 269.

9. Firouzabadi, H.; Afsharifar, G. R., *Bull. Chem. Soc. Jpn*. **1995**, 68, 2602.

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