Tetrahedron Vol. 48, No. 42, pp. 9385-9390, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Stereochemistry of the Addition of Lithiated Methyl Phenyl Sulfoxide to Nitrones

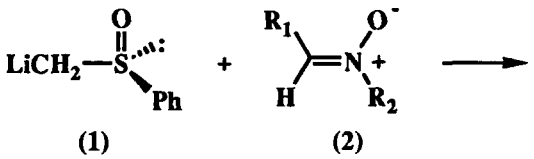
Stephen G. Pyne* and A. R. Hajipour

Department of Chemistry, University of Wollongong, Locked Bag 8844,
South Coast Mail Centre, NSW 2521, Australia.

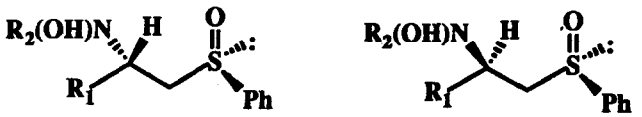
(*Received in UK* 3 *July* 1992)

Abstract: *The stereochemical outcome and diastereoselectivity of the reaction of lithiated methyl phenyl sulfoxide with nitrones is reported. The relative stereochemistry of the major diastereomeric products was determined by chemical correlation with the major diastereomeric products from the reaction of lithiated racemic methyl phenyl sulfoxide with imines.*

We have recently reported the asymmetric synthesis of chiral amines and alkaloids from the addition of lithiated chiral sulfoxides[1] and sulfoximines[2] to prochiral imines. These methods however, work best on diaryl imines (ArCH=NAr) or when the imine is pre-complexed with borontrifluoride etherate.[2b] A similar trend in reactivity has been observed in the addition of other organometallic reagents to imines.[3] On the other hand, nitrones are much more reactive towards addition of organometallic reagents[4]. In 1983, Annunziata and Cinquini[5] reported the addition of lithiated (R) p-tolyl methyl sulfoxide to three nitrones (PhCH=N(O)R, R = CH_3, Ph, Bu^t) at -78°C. The diastereoselectivity of these reactions increased as the steric demand of the R group increased (Me < Ph < Bu^t). No spectral data were reported for the diastereomeric adducts and the stereochemical outcomes of these reactions were not determined. We now report our study on the addition of racemic lithiated methyl phenyl sulfoxide (1) to some representative nitrones and the stereochemistry of the major and minor diastereomeric adducts.

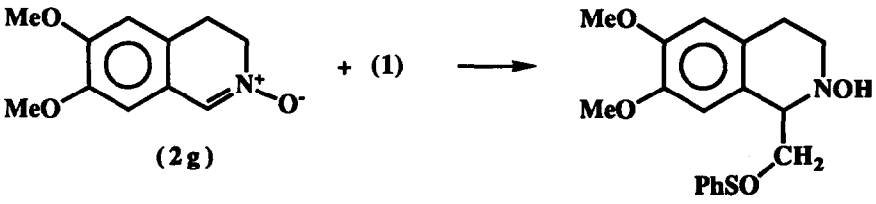


(1) (2)



(3) (4)

Addition of a solution of the nitrones (2) to a solution of (1) at -78°C in THF for 1 hr afforded a mixture of the diastereomeric and racemic β-hydroxyamino sulfoxides, (3) and (4), in good to excellent yields after purification by simple column chromatography (Table 1). The product diastereoselectivities, as determined by ^{1}H NMR analysis on the crude reaction products, ranged from 50 : 50 to 86 : 14. These diastereoselectivities were in general less favourable than those of the analogous reactions of lithiated methyl phenyl sulfoxide with imines.[1] As found previously,[5] for nitrones of the type PhCH=N(O)R, the product diastereoselection increased, although not as dramatically as that reported previously,[5] as the steric demand of the N-substituent of the nitrone increased (Table 1, entries 1-5). The highest product diastereoselection was obtained with the isoquinoline nitrone (2g).



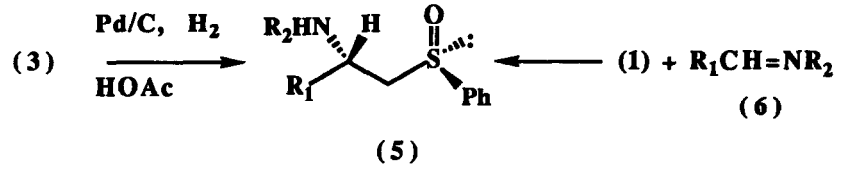
(2g) (3g/4g)

Table 1. Addition of (1) to nitrones (2).

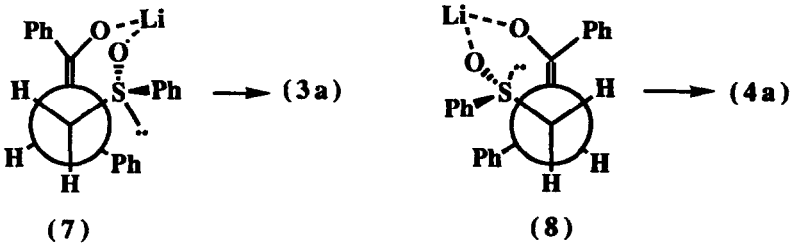
Entry	Nitrone		Yield of	Diastereoselection
	R_1	R_2	(3) and (4) (%)	(3) : (4)
1	(2a), Ph	Me	73	67 : 33
2	(2b), Ph	CH_2Ph	79	75 : 25
3	(2c), Ph	Ph	74	83 : 17
4	(2d), Ph	2-furyl	86	79 : 21
5	(2e), Ph	Bu^t	83	85 : 15
6	(2f), Me	Bu^t	85	50 : 50
7	(2g)		92	86 : 14

The relative stereochemistry of the major diastereomeric products (3c) and (3d) was determined by chemical correlation with (5c) and (5d) respectively, the major diastereomeric products from the reaction of lithiated racemic methyl phenyl sulfoxide with the imines (6) (R=Ph, 2-furyl).[1] Hydrogenolysis of (3c) and (3d) over palladium on carbon in acetic acid and at one atmosphere pressure of hydrogen[4a] gave (5c) and (5d)

respectively, in good yield. It is evident that the addition of lithiated methyl phenyl sulfoxide to nitrones (2c,d) and imines (6) (R = Ph, 2-furyl) occurs with a similar diastereoselection and in the same stereochemical sense.



The stereochemical outcome of the reaction of (1) with imines was rationalised as arising from a chelated chair transition state[1]. The two possible chelated transition states (7) and (8) for the reaction of (1) and nitrone (2c) are shown in Scheme 1. One would expect little difference in free energy between transition states (7) and (8) and consequently the product diastereoselections are only modest to good.



In conclusion, nitrones offer enhanced reactivity over imines towards 1,2-addition of lithiated sulfoxides. Even the dialkyl substituted nitrone (2f) gave products in good yield. In contrast the reaction of (1) with dialkyl imines gives a complex mixture of products. Attempts to improve the diastereoselectivity of these reactions is currently under investigation.

Experimental

The nitrones (2a) and (2b) were prepared by alkylation of anti benzaldehyde oxime[6]. Nitrones (2c)-(2f) were prepared by condensation of the appropriate aldehyde with the appropriate N-hydroxylamine[7]. Nitrone (2g) was prepared by oxidation of 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline with selenium dioxide[8]. All ^{1}H NMR spectra were recorded at 400 MHz and in $CDCl_3$ solution, chemical shifts are given in p.p.m. relative to TMS.

Reaction of (1) with Nitrones (2); A General Procedure:

Methyl phenyl sulfoxide (2.0 mmol) in anhydrous tetrahydrofuran was added dropwise to a cooled (-78°C), stirred solution of LDA, prepared from diisopropylamine (0.58 ml, 4 mmol) and n-butyl lithium (2.45 ml of 1.6 M solution in hexane in THF (5 ml)). The mixture was allowed to reach -20°C, and was then cooled again to -78°C, and treated with a solution of the nitrone (2 mmol) in THF (15 ml). The mixture was stirred for 30 mins. at -78°C and then quenched with NH_4Cl. The mixture was warmed to room temperature and then

extracted with CH_2Cl_2 (2 x 20 ml). The combined extracts were washed with water, dried ($MgSO_4$) and then evaporated to dryness. The crude product was then purified by column chromatography on silica gel using ethyl acetate/hexane (1 : 1) as the eluent. The diastereoselection of these reactions were determined from ^1H NMR (400 MHz) analysis of the crude reaction product.

(R^*_S,1S^*)*N*-Phenyl-*N*-(1-phenyl-2-(phenylsulfinyl))ethylhydroxylamine (3a).

M.p. 162-163°; IR (nujol) 3502, 3320, 1030 cm^{-1}. ^1H NMR 7.68-7.05 (m, 12H), 6.7-6.5 (m, 3H); 5.24 (dd, J = 6.0, 10.8 Hz, 1H), 3.82 (dd, J = 10.8, 14 Hz, 1H), 3.20 (dd, J = 6, 14 Hz, 1H). ^{13}C NMR 153.3, 146.2, 143.8, 141.1, 130.2, 128.1, 126.3, 121.3, 118.6, 114.1, 110.4, 105.3, 60.2, 46.4. MS m/z 337 (100, M^+), 321, 229, 213, 195, 185, 135, 125. Anal calcd for $C_{20}H_{19}NO_2S$: C, 71.2; H, 5.7; H, 6.32; N, 4.4%. Found; C, 71.4; H, 6.3; N, 4.4%.

(R^*_S,1R^*)*N*-Phenyl-*N*-(1-phenyl-2-(phenylsulfinyl))ethylhydroxylamine (4a).

^1H NMR (in part) 4.85 (dd, J=8.4, 12 Hz, 1H).

(R^*_S,1S^*)*N*-phenyl-*N*-(1-(2'-furyl)-2-(phenylsulfinyl))ethylhydroxylamine (3b).

M.p. 152-4°; IR (nujol) 3501, 3166, 1600, 1460, 1030 cm^{-1}. ^1H NMR 7.8-7.15 (m, 8H), 6.82-6.23 (m, 5H), 6.2 (m, 1H), 5.14 (dd, J = 4.8, 10.0 Hz, 1H), 3.76 (dd, J = 10.0, 13.2 Hz, 1H). 3.25 (dd, J = 4.8, 13.2 Hz, 1H). ^{13}C NMR 149.6, 142.2, 141.3, 130.2, 128.5, 127.8, 123.5, 121.8, 116.4, 109.5, 108.5, 58.1, 56.4. MS(CI) m/z 312 ($M+H^+$) , 218, 185 (100), 125. Anal calcd for $C_{18}H_{17}NO_3S$; C, 66.0; H, 5.2; N, 4.3%. Found: C, 65.8; H, 5.4; N, 4.2%.

(R^*_S,1R^*)*N*-phenyl-*N*-(1-(2'-furyl)-2-(phenylsulfinyl))ethylhydroxylamine (4b).

^1H NMR (in part) 5.22 (dd, J = 6.7, 10.5 Hz,1H).

(R^*_S,1S^*)*N*-Methyl-*N*-(1-phenyl-2-(phenylsulfinyl))ethylhydroxylamine (3c).

Oil; IR (film) 3600-3200(br), 3300 (sharp), 1035 cm^{-1}. ^1H NMR 7.52 (d, J = 8.2 Hz, 2H), 7.27 (dd, J = 4, 6.4 Hz, 1H), 4.11 (dd, J = 6.8, 9.6 Hz, 1H), 3.72 (dd, J = 9.6, 13.6 Hz, 1H), 3.05 (dd, J = 6.8, 13.6 Hz, 1H); 2.55(s, 3H). ^{13}C NMR 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 276 (100, $M+H^+$), 229 (32, $M+H^+$- NMeOH), 136 (75), 125 (100).

(R^*_S,1R^*)*N*-Methyl-*N*-(1-phenyl-2-(phenylsulfinyl))ethylhydroxylamine (4c).

^1H NMR (in part) 3.92 (dd J = 4, 6 Hz, 1H); 3.45 (dd, J = 4, 13 Hz, 1H), 3.25 (dd, J = 6, 13 Hz, 1H); 2.51(s, 3H).

(R^*_S,1S^*)*N*-*tert*-Butyl-*N*-(1-phenyl-2-(phenylsulfinyl))ethylhydroxylamine (3d).

M.p. 144-146°; IR (nujol) 3520, 3330, 1030 cm^{-1}. ^1H NMR 8.2 (m, 1H), 7.2-7.8 (m, 9H), 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 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 318 (75, M+H^+), 302 (20), 262 (25). Anal calcd for $C_{18}H_{23}NO_2S$: C, 68.1; H, 7.3; N, 4.4%. Found: C; 68.2; H, 7.4; N, 4.4%.

(R^*_S,1R^*)*N*-*tert*-Butyl-*N*-(1-phenyl-2-(phenylsulfinyl))ethylhydroxylamine (4d).

^1H NMR (in part) 3.64 (dd, J = 10.8, 13.6 Hz, 1H), 3.01 (dd, J = 6.4, 13.6 Hz, 1H), 1.021 (s, 9H).

(R^*_S,1S^*)*N*-Phenyl-*N*-(1-benzyl-2-(phenylsulfinyl))ethylhydroxylamine (3e).

M.p. 159-160°; IR (nujol), 3509, 3330, 2950, 1030cm^{-1} ^1H NMR 7.2-7.8 (m, 15H) 4.36 (dd, J = 5, 7 Hz, 1H), 3.84 (d, J = 13.6 Hz, 1H), 3.68 (d, J = 13.6 Hz, 1H), 3.39 (dd, J = 5, 13.6 Hz, 1H), 3.32 (dd, J = 7, 13.6 Hz, 1H). MS(CI) m/z 352 (M+H^+, 20), 337 (75), 230 (50), 211 (100), 197 (60), 142 (100), 127 (100), 106 (80). Anal calcd for $C_{21}H_{21}NO_2S$; C, 71.8; H, 6.0; N, 4.0%, Found: C, 72.0; H, 6.3; N, 4.0%.

(R^*_S,1R^*)*N*-Phenyl-*N*-(1-benzyl-2-(phenylsulfinyl))ethylhydroxylamine (4e).

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

(R^*_S,1S^*)*N*-Methyl-*N*-(1-*tert*-butyl-2-(phenylsulfinyl))ethylhydroxylamine (3f) and (R^*_S.1R^*) (4f).

Oil; IR (nujol) 3700-3000 (br), 1630, 1050 cm^{-1}. ^1H NMR (on 1 : 1 mixture) 7.7 (m, 2H), 7.5 (m, 3H), 3.82-3.66 (m, 1H), 3.13 (dd, J = 10.0, 13.6 Hz, 0.5H), 3.06 (dd, J = 10.4, 14 Hz, 0.5H), 2.83 (dd, J = 6.4, 14 Hz, 0.5H), 2.73 (dd, J = 4, 13.6 Hz, 0.5H), 1.21 (s, 4.5H), 1.19 (s, 4.5H), 1.18 (d, J = 6.4 Hz, 1.5H). ^{13}C NMR (on a 60 : 40 mixture, the minor isomer is shown in brackets) 144.6 (144.7), 130.5 (130.3), 129.0 (128.9), 124.0 (123.9), 66.4 (64.4), 58.7 (59.3), 52.2 (50.0) 27.1 (26.8), 15.0(15.2). MS(CI) m/z 251 (M+H^+, 50), 234 (100), 169 (80), 142 (100), 127 (60), 111 (90).

1,2,3,4-Tetrahydro-2-hydroxy-6,7-dimethoxy-1-(phenylsulfinyl)isoquinoline (3g).

M.p. 155-156°; IR (nujol) 3630-3150, 3400(sharp), 1115, 1032 cm^{-1}. ^1H NMR (in part) 7.78 (dd, J = 2, 7.6 Hz, 1H), 7.45 - 7.65 (m, 4H), 6.63 (s, 1H), 6.47 (s, 1H), 4.45 (dd, J = 4.8, 6.0 Hz, 1H) 3.86 (s,3H), 3.79 (s, 3H), 3.53 (dd, J = 4.8, 14 Hz, 2H), 3.30 (dd, J = 6.0, 14 Hz, 1H), 3.2 (t, 2H), 3.12 (dd, J = 5.2, 8.8, 1H). ^{13}C NMR, 148.2, 147.7, 144.6, 131.3, 130.9, 129.4, 129.3, 127.1, 126.1, 125.0, 123.9, 111.4, 109.3, 64.8, 62.5, 56.1, 52.13, 55.8, 27.0. MS(CI) m/z 338 (25, M+H^+), 205 (30), 192 (29), 154 (100), 136 (100). Anal calcd for $C_{18}H_{21}NO_4S$; C, 62.2; H, 6.1, N, 4.0%. Found: C, 62.0; H, 6.2; N, 4.0%.

1,2,3,4-Tetrahydro-2-hydroxy-6,7-dimethoxy-1-(phenylsulfinyl)isoquinoline (4g).

^{1}H NMR (in part) 6.61 (s, 1H), 6.44 (s,1H), 4.41 (br, 1H), 3.84 (s, 3H), 3.78 (s, 3H).

Hydrogenolysis of (3c) and (3d) to (5c) and (5d)

A mixture of the hydroxylamine (3c or 3d) (1.0 mmol), 10% palladium on charcoal (676 mg) and acetic acid was stirred vigorously under an atmosphere of hydrogen at room temperature for 60 hrs. The catalyst was then separated by filtration through celite and the filtrate was then evaporated under reduced pressure. The residue was dissolved in 1M HCl (10 ml) and the solution was washed with ether (5 ml). The aqueous layer was made basic with 8M NaOH and the solution was extracted with dichloromethane (3 x 5 ml). The combined organic extracts were dried (Na_2SO_4), filtered and then evaporated to dryness to give (5c or 5d) in 65-70% yield. This material was judged to be > 95% pure from ^{1}H NMR analysis. The ^{1}H NMR spectra of (5c) and (5d) were identical to the ^{1}H NMR spectra of the major diastereoisomer products prepared from the reaction of (1) and the imine (6).[1]

Acknowledgement

Partial support of this work by the Australian Research Council is gratefully acknowledged.

References

1. Pyne, S. G.; Dikic, B. *J. Org. Chem.* **1990**, *55*, 1932.
2. (a) Pyne, S. G.; Dikic, B. *Tetrahedron Lett.* **1990**, *31*, 1990.
   (b) Pyne, S. G.; Dikic, B.; Skelton, B.W.; White, A. H. *Aust. J. Chem.* **1992**, *45*, 807.
3. Takahashi, H.; Suzuki, Y.; Inagaki, H. *Chem. Pharm. Bull.* **1982**, *30*, 3160.
4. (a) Hamdouchi, C. *Tetrahedron Lett.* **1992**, *33*, 1701.
   (b) Chang, Z-Y; Coates, R M. *J. Org. Chem* . **1990**, *55*, 3464 and references cited therein.
5. Annunziata, R.; Cinquini, M. *Synthesis* , **1982**, 929.
6. Beuhler, E. *J. Org. Chem.* **1967**, *32*, 261.
7. Heffinger, N F; Griffin, C E; *Tetrahedron Lett.* **1963**, *21*, 1361.
8. Murahashi, S.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 2383.