Pergamon

Tetrahedron Letters, Vol. 35, No. 4, pp. 645-648, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0299-Y

A Convenient Synthesis of 2-Methoxy-1-Naphthyl Sulfoxides in High Enantiomeric Purity. A New Asymmetric Synthesis of 1-Benzyl-1,2,3,4-tetrahydroisoquinolines†

Stephen G. Pyne,* A. R. Hajipour and K. Prabakaran
Department of Chemistry, University of Wollongong, Wollongong, NSW, 2522, Australia

Abstract: The synthesis of diastereomerically pure (-)-(S) menthyl 2-methoxy-1-naphthalenesulfinate (5) is reported. The reaction of (5) with methylmagnesium iodode or benzylmagnesium chloride gives (+)-(R) methyl and (+)-(R) benzyl 2-methoxy-1-naphthyl sulfoxide, (7) and (8) respectively, in high enantiomeric purity (98% ee). Lithiated (8) undergoes addition to 6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide (2) to give a 1-benzyl-1,2,3,4-tetrahydroisoquinoline derivative (9) with high product diastereoselection (d. r. 96 : 4). The stereochemistry of (9) was determined by a single crystal X-ray structure determination.

Sulfoxides are versatile compounds for organic synthesis and asymmetric synthesis.[1] The 1,2- and 1,4-addition reactions of traditional lithiated alkyl and benzyl *p*-tolyl sulfoxides to carbonyl compounds and Michael acceptors however, is generally poorly diastereoselective.[1] We and others have shown that a much improved diastereoselection can be achieved when sterically hindered versions of these sulfoxides are employed.[2] Unfortunately the latter sulfoxides are not readily prepared in high enantiomeric purity and therefore their use in asymmetric synthesis has been limited.[3] In this paper we report a convenient method for the synthesis of (+)-(R) methyl 2-methoxynaphthyl sulfoxide and (+)-(R) benzyl 2-methoxynaphthyl sulfoxide in high enantiomeric purity and the use of the latter sulfoxide in the asymmetric synthesis of a 1-benzyl-1,2,3,4-tetrahydroisoquinoline in high diastereomeric purity.

As part of a project aimed at the asymmetric synthesis of 1-benzyl-1,2,3,4-tetrahydroisoquinolines we have examined the addition of lithiated, racemic benzyl sulfoxides to 6,7-dimethoxy-3,4-dihydroisoquinoline (1) and 6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide (2). The addition of lithiated benzyl sulfoxides to (1)·BF_3 -etherate complex at -78°C gave adducts in low yields (40-45%) and as a mixture of three or four diastereoisomers. The highly hindered benzyl *t*-butyl sulfoxide failed to give any addition products. The cyclic nitrone (2) was, as expected, more reactive and gave mixtures of two of the four possible diastereoisomeric adducts (3) (Table). The best diastereoselection was achieved with with benzyl t-butyl sulfoxide (Table, entry 3), although this was modest and almost identical to that from benzyl methyl sulfoxide (Table, entry 2).

In 1985, Bell[4] reported a convenient synthesis of 2-methoxy-1-naphthalenesulfinyl chloride (4) from the chlorosulfination of 2-methoxynaphthalene with thionyl chloride. We have found that (4) can be converted to a mixture (*ca* 1 : 1)) of (-)-(S) menthyl 2-methoxy-1-naphthalenesulfinate (5) and (+)-(R) menthyl sulfinate (6), as shown in Scheme 1. The less soluble diastereoisomer, (-)-(S) (5), can be obtained diastereomerically pure by selective crystallization from acetone. Diastereomerically pure (5) can be obtained in 73% overall yield by successive treatment of the mother liquors with a few drops of concentrated hydrochloric acid (to effect epimerization at sulfur) and further recrystallization from acetone according to the method developed by Solladie.[5] The relative stereochemistry of (5) was determined by a single crystal X-ray

structural determination.[6] Treatment of (5) with methylmagnesium iodide or benzylmagnesium chloride in ether/benzene at room temperature[7] gave (+)-(R) methyl 2-methoxy-1-naphthyl sulfoxide (7) and (+)-(R) benzyl 2-methoxy-1-naphthyl sulfoxide (8), respectively. The enantiomeric purity of these compounds was determined to be 98% from ^{1}H NMR shift studies using (-)-(R)-*N*-(3,5-dinitrobenzoyl)-α-phenylethylamine as a chiral shift reagent.[8]

The addition of lithiated (8) to the nitrone (2) at -78°C was highly diastereoselective (d.r. = 96 : 4) and gave the desired adduct (9) in 63% yield after purification by column chromatography. The (1S, 1'S, *S*R) stereochemistry of the major diastereomeric product was elucidated by single crystal X-ray structural analysis.[6] The stereochemical outcome of this reaction can be rationalized as arising from the lithium chelated intermediate (10). By analogy with the known solid state structures of lithiated sulfoxides,[9] the phenyl and 2-methoxy-1-naphthyl rings would be expected to have a trans disposition in lithiated (8) in order to minimize steric repulsions. The π-facial selectivity with respect to addition of the anion to the nitrone (2) would be expected as shown in (10) to minimize steric interations between the sulfoxide ion and the ring system of the nitrone. The 2-methoxy group in lithiated (8), by increasing the the Lewis basicity of the sulfoxide oxygen, may also be responsible for the high diastereoselectivity in its reactions with (2).[10]

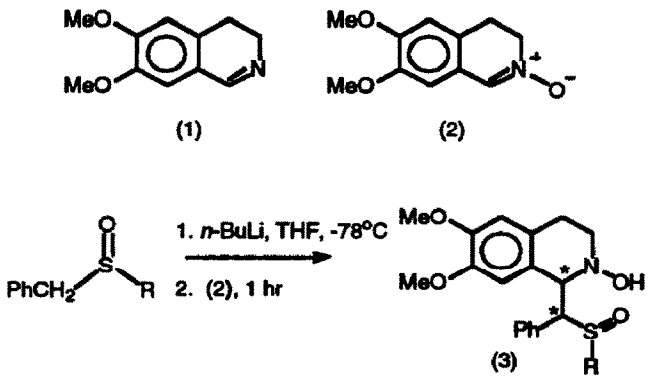


Table. Addition of lithiated benzyl sulfoxides to (2).

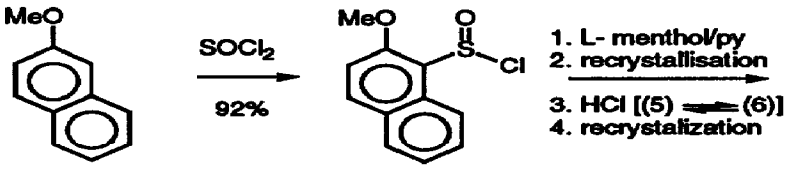
Entry	Sulfoxide R	Diastereomeric Ratio of (3)[a]	Yield (%) of (3)[b]
1	Ph	56 : 44	64
2	Me	76 : 24	71
3	Bu^t	78 : 22	60
4	(+)-(R) (8)	96 : 4	63[c]

[a] From ^{1}H NMR (400 MHz) analyses of the crude reaction mixture.

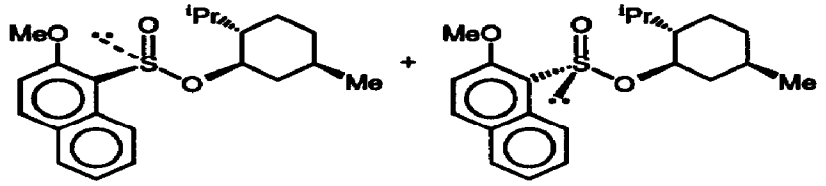
[b] After purification by column chromatography. [c] Starting (8) was also recovered.

In summary, we have developed an efficient method for the synthesis of sterically hindered sulfoxides in high enantiomeric purity. Sulfinate (5) should be an extremely useful compound to prepare other sterically

Scheme 1

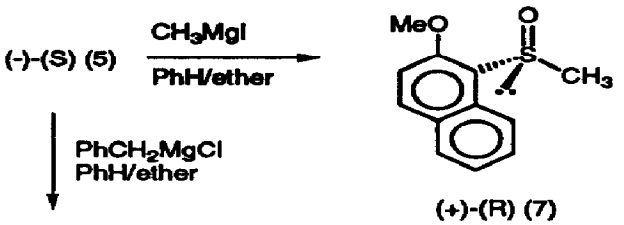


(4)



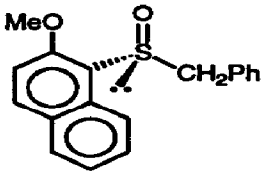
(-)-(S) (5) (+)-(R) (6)

yield: 73%
m.p. 103°C
$[\alpha]_D^{26}$ -183 (c 1.2, $CHCl_3$)



(+)-(R) (7)

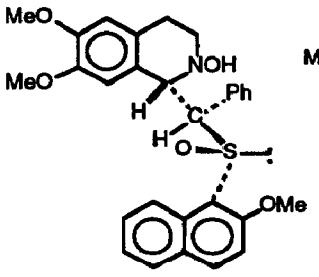
yield: 76%
m.p. 102-3 °C
$[\alpha]_D^{22}$ +107 (c ,0.1, $CHCl_3$)
e.e. 98%



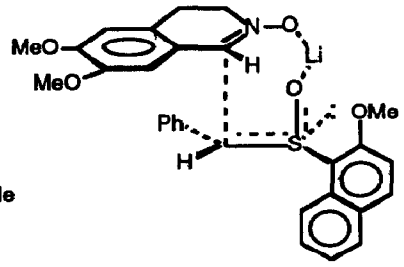
(+)-(R) (8)

yield: 58%
m.p. 112°C
$[\alpha]_D^{26}$ +44 (c 0.1, $CHCl_3$)
e.e. 98%

hindered sulfoxides that would be useful for asymmetric synthesis. The application of (5) towards these goals is currently under active investigation.



(-)-(1S, 1'S, SR) (9)
m.p. 121-2°C
$[\alpha]_D^{21}$ -24 (c 0.11, $CHCl_3$)



(10)

(-)-(S) (L) Menthyl 2-methoxy-1-naphthalenesulfinate (5).
To a stirred solution of L-menthol (0.17 mol) in dry CH_2Cl_2 (350 mL) at 0°C was added a solution of (4)[4] (0.17 mol) in CH_2Cl_2 (100 mL) dropwise over 10 min. Pyridine (13.4g, 0.17 mol) was then added and the mixture was stirred at 0°C for 2 hr and then at room temperature overnight. The reaction mixture was then filtered and the clear solution was washed with 10% aqueous HCl (100 mL), dried ($MgSO_4$) and then the solvent was removed under reduced pressure. The residue was dissolved in acetone (10 mL) and allowed to crystallise at 5°C. The crystals were collected by vacuum filtration. To the mother liquor was added two drops of concentrated HCl and a second crop of crystals were collected after crystallisation at 5°C. This process was repeated a futher two times and gave (5) in a combined yield of 73% yield; m.p. 103°C, $[\alpha]_D^{26}$ - 183 (c 1.2, $CHCl_3$). Anal. Calcd for $C_{21}H_{27}O_3S$: C, 69.96; H, 7.99; S, 8.89. Found: C, 69.68; H, 7.82; S, 8.49.

References

†Chiral Sulfur Compounds, Part 24.

1. For a recent review, see: Walker, A. J., *Tetrahedron: Asymmetry*, **1992**, *3*, 961-998.
2. (a) Sakuraba, H.; Ushiki, S., *Tetrahedron Lett.*, **1990**, *31*, 5349-5352. (b) Pyne, S. G.; Boche, G., *J. Org. Chem.*, **1989**, *54*, 2663-2667. (c) Casey, M.; Manage, A. C.; Nezhat, L., *Tetrahedron*, **1988**, *29*, 5821-5824. (d) Demailly, G.; Greck, C.; Solladie, G., *Tetrahedron Lett.*, **1984**, *25*, 4113-4116.
3. For a recent method of preparing alkyl t-butyl sulfoxides in high enantiomeric purity see: Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D., *J. Am. Chem. Soc.*, **1992**, *114*, 5977-5985.
4. Bell, K. H., *Aust. J. Chem.*, **1985**, *38*, 1209-1221.
5. Mioskowski, C.; Solladie, G., *Tetrahedron*, **1980**, *36*, 227-236.
6. Pyne, S. G.; Prabakaran, K.; Skelton, B. W.; White, A. H., unpublished results.
7. Drabowsicz, J.; Bujnicki, B.; Mikolajczyk, M., *J. Org. Chem.* **1982**, *47*, 3325-3327.
8. Deshmukh, M.; Dunach, E.; Kagan, H. B., *Tetrahedron Lett.*, **1984**, *25*, 3467-3470.
9. Boche, G., *Angew. Chem. Int. Ed. Engl.*, **1989**, *28*, 277-297.
10. Posner, G. H.; Frye, L. L.; Hulce, M., *Tetrahedron*, **1984**, *40*, 1401-1407.

Acknowledgment: Financial support from the Australian Research Council is gratefully acknowledged.

(*Received in UK* 15 *October* 1993; *accepted* 26 *November* 1993)