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A NEW AND CONVENIENT PROCESS FOR PREPARATION OF OPTICALLY PURE ARYL 2-PYRIDYL SULFOXIDES

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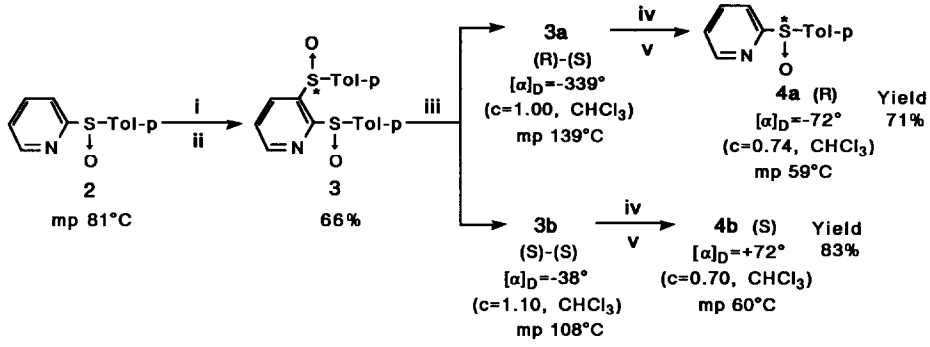
Abstract: α-Lithiation of aryl 2-pyridyl sulfoxides, treatment with ℓ-menthyl sulfinate, and desulfinylation with Grignard reagents gave optically pure aryl 2-pyridyl sulfoxides in moderate yields.

Optically active sulfoxides have been widely used as chiral sources for asymmetric synthesis. Among the several known preparative methods of optically active sulfoxides, Andersen's procedure (the reactions of optically active sulfinates with Grignard or organolithium reagents) is the simplest and most useful for the preparation of common optically pure sulfoxides.[1] On the other hand, there are a few reports for preparation of optically active sulfoxides bearing azaheterocycles, i.e., pyridine or quinoline. One is the asymmetric oxidation of methyl 2- and 4-pyridyl sulfides using Sharpless oxidation method[2] while we reported that the reactions of 3- and 4-pyridyl Grignard reagents with (+)-(R) *p*-tolyl ℓ-menthyl sulfinate (**1**) to give optically pure pyridyl sulfoxides in good yields.[3] However, this Andersen's process was unsuccessful to prepare 2-pyridyl isomer since when 2-pyridyl Grignard reagent[4] was treated with the sulfinate **1**, the coupling product, 2-(ℓ-menthoxy)pyridine, was obtained in 67% yield as a sole product instead of getting the desired 2-pyridyl sulfoxide.

After several trials, we found that the initial treatment of 3-lithiated aryl 2-pyridyl sulfoxides with Andersen's ester 1 and subsequent desulfinylation with Grignard reagent became a convenient synthetic method for optically pure aryl 2-pyridyl sulfoxides. This communication reports the first synthetic method of optically pure aryl 2-pyridyl sulfoxides.

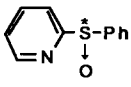
When 2-pyridyl *p*-tolyl sulfoxide (**2**) was treated with LDA[5] and subsequently with **1** to give 2,3-bis(*p*-tolylsulfinyl)pyridine (**3**) in 66% yield. The bis-sulfoxide **3** contained two diastereomers [(R)-(S), less polar compound **3a** and (S)-(S), more polar compound **3b**] which were readily separated to each isomer by column chromatography (silicagel, n-hexane/ethylacetate =1/1). Isomer **3a** was treated with *p*-tolyl Grignard reagent and then with water to give (-)-(R) 2-pyridyl *p*-tolyl sulfoxide (**4a**) and di(*p*-tolyl)sulfoxide in 71 and 78% yields respectively. The substitution reaction was observed only at the sulfinyl group attached at the 3-position in the pyridine ring. Similarly, the isomer **3b** was treated with *p*-tolyl Grignard reagent to give (+)-(S) 2-pyridyl *p*-tolyl sulfoxide (**4b**) in 83% yield. The absolute configurations of the sulfoxides obtained were assigned by comparison of their optical rotations with (+)-(S) 3- or 4-pyridyl *p*-tolyl sulfoxides reported previously.[3] The structures were identified by comparing the spectrum data with those of the authentic sulfoxides.[6] Their optical purities were determined by liquid chromatography using chiral cell OB-1 (Daicel Co.). The results are shown in Scheme 1.



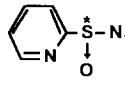
i: LDA, THF, -78°C; ii: p-Tol-S(O)-Ment-ℓ, -95°C; iii: separation by column chromatography; iv: p-TolMgBr, THF, -90°C; v: H_2O.

Scheme 1

Furthermore, on similar treatment as described above, racemic phenyl and 1-naphthyl 2-pyridyl sulfoxides were converted to the corresponding optically pure sulfoxides in about 40% total yields. Their optical rotations of the sulfoxides obtained are shown as below. The physical properties were consistent with the authentic samples prepared elsewhere. The absolute configurations of 1-naphthyl 2-pyridyl sulfoxides obtained were assigned tentatively by comparison of their optical rotations with those of optically pure 1-naphthyl *p*-tolyl sulfoxides reported previously.[1)]



(R) $[\alpha]_D$=-41° (c=1.02, $CHCl_3$)
(S) $[\alpha]_D$=+42° (c=1.00, $CHCl_3$)
mp 73°C Total yield 38%



(R) $[\alpha]_D$=-434° (c=1.10, $CHCl_3$)
(S) $[\alpha]_D$=+430° (c=1.28, $CHCl_3$)
oil Total yield 37%

A combination of these reactions will be promised to become a convenient preparation of various optically pure aryl 2-pyridyl and other azaheteroarylic sulfoxides which are hardly to prepare by conventional methods. Further work is now in progress in this laboratory.

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References and Notes

1) a) K. K. Andersen, *Tetrahedron Lett.*, **1962**, 93; b) K. K. Andersen, W. Gaffield, N. E. Papanikolaou, J. W. Foley, and R. I. Perkins, *J. Am. Chem. Soc.*, **86**, 5637 (1964); c) C. Mioskowski and G. Solladié, *Tetrahedron Lett.*, **1975**, 3341. 2) a) P. Pitchen, E. Duñach, M. N. Deshmukh, and H. B. Kagan, *J. Am. Chem. Soc.*, **106**, 8188 (1984); b) U. Bortolini, F. DiFuria, G. Licini, and G. Modena, "Reviews of Heteroatom Chemistry" Vol. 1, p. 66, Ed. S. Oae, Tokyo, (1988). 3) N. Furukawa, T. Shibutani, K. Matsumura, H. Fujihara, and S. Oae, *Tetrahedron Lett.*, **27**, 3899 (1986). 4) N. Furukawa, T. Shibutani, and H. Fujihara, *Tetrahedron Lett.*, **28**, 5845 (1987). 5) N. Furukawa, T. Shibutani, and H. Fujihara, *Tetrahedron Lett.*, **30**, 7091 (1989). 6) **4a** and **4b**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.34 (s, 3H, CH_3), 7.25 (d, 2H, Ar-H, J=8.0 Hz), 7.27 (ddd, 1H, 5-Py-H, J=1.0, 4.9, 7.6 Hz), 7.67 (d, 2H, Ar-H, J=8.0 Hz), 7.87 (ddd, 1H, 4-Py-H, J=1.0, 7.6, 7.8 Hz), 8.05 (dd, 1H, 3-Py-H, J=1.0, 7.8 Hz), 8.54(dd, 1H, 6-Py-H, J=1.0, 4.9 Hz); ^{13}C-NMR ($CDCl_3$) δ 21.3, 118.3, 124.5, 125.0, 129.8, 138.0, 140.7, 141.3, 149.7, 165.6; IR (KBr) 1046 cm^{-1} (S-O); MS m/z 217 (M^+), 201 (M^+-O).

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