An Improved and Efficient Preparation of the Chiral NAD(P)H Model (S_S)-1-Benzyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine

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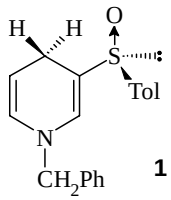
Abstract: An improved procedure for the preparation of chiral NAD(P)H model, (S_S)-1-benzyl-3-(p-tolylsulfinyl)-1,4-dihydropyridine, with satisfactary chemical yield and excellent enantiopurity is reported.

Keywords: Chiral NAD(P)H models, (S_S)-1-benzyl-3-(p-tolylsulfinyl)-1,4-dihydropyridine.

Chiral NAD(P)H models are important reduction reagents in asymmetric synthesis. (S_S)-1-Benzyl-3-(p-tolylsulfinyl)-1,4-dihydropyridine **1** is one of these models, which can reduce carbonyl and unsaturated compound under mild conditions with high enantioselectivity[1]. An impressive example is that methyl benzoylformate is reduced by **1** in the presence of Mg^{2+} or Zn^{2+} to methyl (R)-mandelate with up to 97% e.e. at room temperature[2]. Our investigation[3] has shown that the reduction of allylic bromide by **1** without Mg^{2+} or Zn^{2+} produces the cyclopropane product[4] with moderate enantioselectivity.



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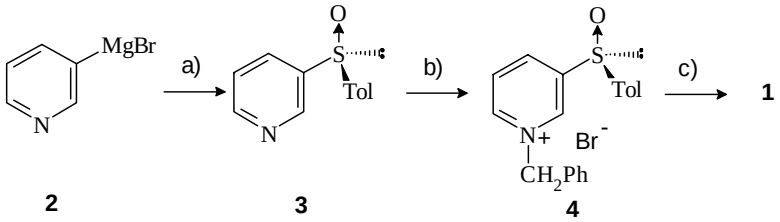
However, as we prepared **1** according to a literature method[5], the overall chemical yield was very low. Some modifications of the two main steps have been made to improve the chemical yields and compound **1** was obtained with high purity in high yields. Herein we report the results.

Compound **1** was prepared according to literature 5 by the following procedure (**Scheme 1**):

Scheme 1



a) Solution of 3-pyridylmagnesium bromide in dry THF-ether[6] was dropped into solution of (-)-menthyl(S)-p-tolylsulfinate in dry THF at -78℃, and the mixture stirred at -78℃ for 1 hour, 87% yield.
b) Heated with $PhCH_2Br$ in toluene overnight, 87% yield.
c) Reduced by aqueous $Na_2S_2O_4$ in CH_2Cl_2 and 1 N $NaHCO_3$, 49% yield

When we repeated the experiment under exactly the same conditions as reported[5], we did obtain product **3** of 100% e.e. but the chemical yield was very low (10%). However, when either the solution of 3-pyridyl-magnesium bromide was dropped to the solution of (-)menthyl(S)-p-tolylsulfinate or *vice versa* at 0℃ instead of -78℃, the chemical yields increased to about 90%. Since 3-pyridyl-magnesium bromide solution is air-sensitive, we then tried to add the solution of (-)-menthyl(S)-p-tolylsulfinate to the solution of 3-pyridyl-magnesium bromide at -78℃, and slowly raised the reaction temperature to -30℃ during the period of 5 h. The high chemical yield of 80% was obtained and the enantiopurity of the compound **3** was found to be 100%e.e. by HPLC analysis using a Daicel chiralcel OB column[7].

In the reduction of compound **4** to **1**, **4** was reduced by 1-propyl-1,4-dihydronicotinamide in methanol[8] instead of aqueous $Na_2S_2O_4$. The product **1** could be obtained in about 90% chemical yield with high purity after purification once by silicon-gel column chromatograghy. It is noteworthy that the optical rotation of the product was higher than that reported, $[\alpha]^{24}_D$= +208.7 ($CHCl_3$, c=0.25)[9] (literature 5, $[\alpha]^{24}_D$= +160.8, $CHCl_3$, c=0.25).

In conclusion, a modified procedure for the preparation of compound **1** is reported which not only improves the yields but also produces an optically active product with higher specific rotation.

Expermental

^1H NMR spectra were obtained on a Bruker AM-200 spectrometer using $CDCl_3$ as solvent and TMS as internal reference. Mass spectra were determined on a VG 7070E GC/MS/DS mass spectrometer (EI). Elemental analysis were carried out with a Carlo Erba-1160 elemental analytical apparatus.

(S_S)-3-(p-Tolylsulfinyl)pyridine 2: A solution of 3-pyridylmagnesium bromide in dry THF-ether (0.125M, 16ml, 2mmol) prepared according to literature 6 was stirred at

-78℃. To this solution a solution of menthyl-(S)-p-toluenesulfinate (500mg, 1.7mmol) in 4 ml dry THF was added dropwise. The reaction mixture was stirred at -78℃ for 1 h and then the reaction temperature was slowly raised to -30℃ during a period of 5 h. The reaction mixture was treated with saturated aqueous NH_4Cl and extracted with ether. Usual work-up and purification by SiO_2 column chromatography [AcOEt-hexane (4:1)] gave **2** as light yellow solid (273 mg, 80% yield, 100%e.e.). ^{1}H NMR δ ppm 2.38 (3H, s), 7.30, 7.55 (4H, AA'BB' type, *J*=8Hz), 7.42 (1H, dd, *J*=8.0, 4.8Hz) , 8.01 (1H, d, *J*=8.0Hz), 8.67 (1H, dd, *J*=4.8, 1.0Hz), 8.76 (1H, d, J=2.0Hz); MS (m/z): 217(M^+), 201, 200.

(S_S)-1-Benzyl-3-(p-tolylsulfinyl)-1,4-dihydropyridine 1: A mixture of **4** (194mg, 0.5mmol) and 1-propyl-1,4-dihydronicotinamide (94mg, 0.6mmol) in 2ml dry CH_3OH was stirred at 30℃ for 12 h in the dark under Ar atmosphere. The solvent was removed under reduced pressure. The residue was purified by SiO_2 column chromatography [hexane-AcOEt-Et_3N (20:10:3)] to give **1** (142mg) as yellowish solid in 92% yield. ^{1}H NMR δ ppm 2.34 (3H, s), 2.38 (1H, dm, *J*=17.6Hz), 3.06 (1H, dm, *J*=17.6Hz), 4.24 (2H, s), 4.54 (1H, dt, *J*=8.0, 3.5Hz), 5.63 (1H, dq, *J*=8.0, 1.6Hz), 6.71 (1H, d, *J*=1.3Hz), 7.21 (5H, brs), 7.31, 7.41 (4H, AA'BB' type, *J*=6.4Hz); Anal. Calcd for $C_{19}H_{19}NOS$: C, 73.98; H, 6.12; N, 4.53; Found: C, 74.03; H, 6.17; N, 4.62.

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7. The detecter wavelength: 254nm; flow rate: 0.8ml/min; solvent system: i-PrOH/hexane, 10/90; retention time of (+)-(**3**): 40.73min; retention time of (-)-(**3**): 46.36 min.
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9. Optical rotation was recorded in $CHCl_3$ at 25℃ on a PE polarimeter 341 instrument.

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