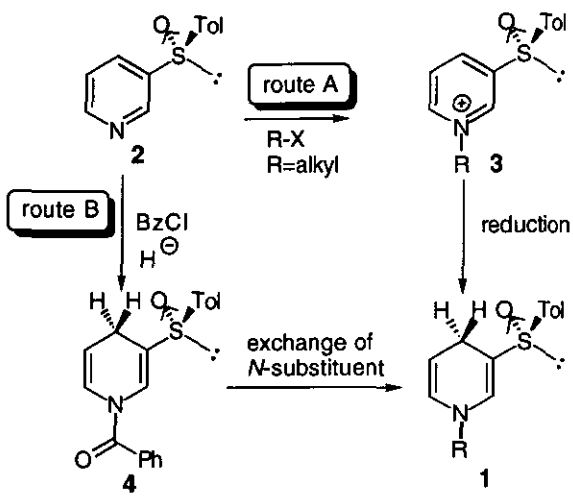
SYNTHESES OF 1-SUBSTITUTED (S_S)-3-*p*-TOLYLSULFINYL-1,4-DIHYDROPYRIDINES, CHIRAL NADH MODEL COMPOUNDS[1]

Satoshi Obika, Toshihiko Nishiyama, Satoshi Tatematsu, Masahiro Nishimoto, Kazuyuki Miyashita, and Takeshi Imanishi*

Faculty of Pharmaceutical Sciences, Osaka University
1-6 Yamadaoka, Suita, Osaka 565, Japan

Abstract - (S_S)-3-(*p*-Tolylsulfinyl)-1,4-dihydropyridines with various kinds of substituents on the N-1 position were synthesized from (S_S)-1-lithio-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine, which was generated on reaction of the 1-benzoyl derivative with methyllithium.

In the previous papers, we reported the synthesis of novel chiral NADH model compounds, (S_S)-1-alkyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridines (**1**) and the successful application to asymmetric reduction of methyl benzoylformate.[1,2] The utilized synthetic route for **1** consisted in quaternization of the sulfinylated pyridine (**2**) with alkyl halides or dialkyl sulfate and subsequent partial reduction of the pyridinium salts (**3**) (route A). In this route, however, variation of the 1-substituents was limited to only some simple alkyl groups. In addition, 1-unsubstituted 1,4-dihydropyridine (**1**, R=H) is of interest since it is expected to be highly reactive and, as a consequence, could serve as a novel type of NADH model compound. However, due to labile property of this type of compounds, only a few examples for isolation have been reported.[3,4] The need for further application and mechanistic study of asymmetric reduction with this series of 1,4-dihydropyridine compounds prompted us to investigate an alternative and convenient method for preparation of the dihydropyridines (**1**) with various substituents on the ring nitrogen atom.

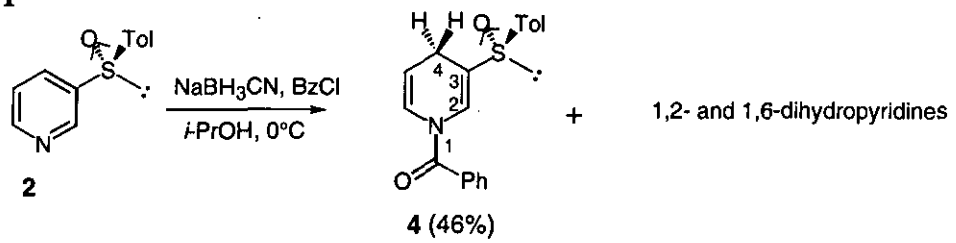


This paper is dedicated to Professor Shigeru Oae on the occasion of his 77th birthday.

In this paper, we wish to describe the versatile method of synthesis of 3-(*p*-tolylsulfinyl)-1,4-dihydropyridines with various kinds of substituents on the N-1 position *via* reductive acylation of **2** followed by exchange of the substituent of the N-1 in **4**, as shown in route B.

Since 1-acyl substituents were known to stabilize the labile dihydropyridine structure,[4] a reductive acylation of the pyridine (**2**) is expected to give a stable 1-acyl-1,4-dihydropyridine as a suitable key-intermediate for the target molecules (**1**) with various substituents at the 1-position. After several attempts,[5] 1-benzoyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine (**4**) was found to be obtainable as a main product by treatment of **2** with sodium cyanoborohydride and benzoyl chloride as shown in Scheme 1.

Scheme 1



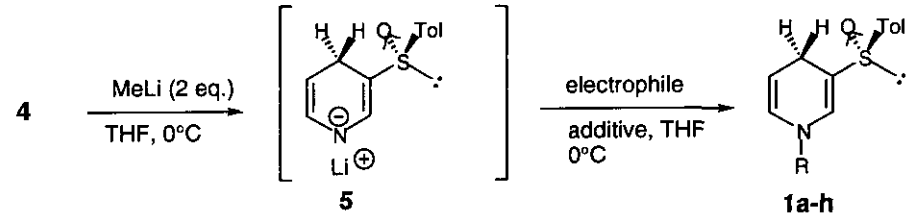
2

4 (46%)

Next, exchange of the 1-substituent in **4** was examined. Fowler *et al.* reported that 1-methoxycarbonyl-1,4-dihydropyridine gave the unsubstituted 1,4-dihydropyridine upon the reaction with 3 equiv. of methyllithium.[4] When the 1-benzoyldihydropyridine (**4**) was treated with 2 equiv. of methyllithium in THF at 0°C and subsequently quenched by addition of water, the desired 1-unsubstituted 1,4-dihydropyridine (**1a**) was obtained in 79% yield as colorless crystals. Generally, 1-unsubstituted dihydropyridines are so unstable that it is difficult to be isolated as a pure form.[3,4] This encouraged us to examine the reactions of the 1-lithio intermediate (**5**) with several electrophiles and the results are summarized in Table 1. Alkylation of the intermediate (**5**) with propyl bromide and benzyl bromide gave the corresponding 1-alkyl-1,4-dihydropyridines (**1b**) and (**1c**) (Runs 2 and 4), both of which had been already synthesized *via* route A.[1] In this reaction, racemization of the sulfinyl group and transposition of the double bond were not observed at all by comparison with the spectral data of the authentic samples. Addition of HMPA to the reaction mixture increased the yields of the alkylation reactions (Runs 2-7). Compounds (**1d**) and (**1e**) are of great interest as novel type of NADH models having a hetero atom substituted carbon center similarly to that of an anomeric center of NAD(P)H, since the conformation of 1,4-dihydropyridine ring of NAD(P)H is known to be restricted by the anomeric effect to contribute to the stereospecificity of the reduction with NAD(P)H in enzymatic system.[6] Various carbamoyl protecting groups [*t*-butoxycarbonyl (Boc) group, trimethylsilylethoxycarbonyl (Teoc) group[7] and allyloxycarbonyl (Alloc) group[8]] were also successfully introduced to the nitrogen of 1,4-dihydropyridine ring in good yields by employing the same method (Runs 8-10). Since these protecting groups can be removed under

mild conditions,[9] these compounds (**1f-h**) are expected to work as a stable and potent NADH model which can generate the reactive 1,4-dihydropyridine (**1a**) *in situ*.

Table 1. Syntheses of various 1-substituted 1,4-dihydropyridines (1) from **4** *via* **5**



Run	Electrophile	Additive	Time	Product	R	Yield %
1	H_2O (excess)	———	10 min	**1a**	H	79
2	Pr-Br (1.5 eq.)	———	24 h	**1b**	Pr	29
3	Pr-Br (1.5 eq.)	HMPA (5eq.)	6 h	**1b**	Pr	51
4	Bzl-Br (1.5 eq.)	———	3 h	**1c**	Bzl	77
5	Bzl-Br (1.5 eq.)	HMPA (5eq.)	2 h	**1c**	Bzl	91
6	MOM-Cl (1.5 eq.)	HMPA (2eq.)	1 h	**1d**	MOM	90
7	MEM-Cl (1.5 eq.)	HMPA (2eq.)	1 h	**1e**	MEM	79
8	Boc_2O (1.2 eq.)	———	2 h	**1f**	Boc	100
9	Teoc-Imd (1.2 eq.)[a]	———	1 h	**1g**	Teoc	86
10	Alloc-Imd (1.0 eq.)[b]	———	1 h	**1h**	Alloc	76

a) Trimethylsilylethoxycarbonylimidazole. *b*) Allyloxycarbonylimidazole.

In conclusion an efficient method for synthesis of various 1-substituted 1,4-dihydropyridines (**1a-h**) *via* 1-acyl derivative (**4**) was developed.

EXPERIMENTAL SECTION

All melting points measured on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (ir) spectra were recorded on a JASCO FT/IR-200 spectrophotometer, and ^{1}H-nmr spectra on a Varian VXR-200 (200 MHz), JEOL EX-270 (270 MHz) or JEOL GX-500 (500 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. Low resolution mass spectra (ms) were obtained with a Shimadzu GCMS-QP1000 or a JEOL JMS-D300 instrument, and high resolution mass spectra (High ms) with a JEOL JMS-D300 instrument. $[\alpha]_D$ Values were recorded on a JASCO DIP-370 instrument. For column chromatography, Merck Kieselgel 60 (0.063-0.200 mm) was used. Trimethylsilylethoxycarbonylimidazole was prepared according to the literature[10] and allyloxycarbonylimidazole was prepared by the similar method.

(S_S)-1-Benzoyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine (4). To a solution of (S_S)-3-(*p*-tolylsulfinyl)-pyridine (100 mg, 0.46 mmol) in dry 2-propanol (10 ml) were added $NaBH_3CN$ (15 mg, 0.24 mmol) and

benzoyl chloride (70 μl, 0.60 mmol) under an argon atmosphere at 0°C. After stirring was continued for 90 min in the dark, water (2 ml) was added and the whole was stirred for 10 min. The solution was concentrated, and the residue was diluted with CH_2Cl_2. The organic layer was washed with water and brine and dried over Na_2SO_4. Filtration and concentration gave the crude product, which was purified by SiO_2 column chromatography [AcOEt-hexane (1:2)] to give **4** (65 mg, 46%) as a white solid. Analytical sample was obtained by recrystalization from CH_2Cl_2-Et_2O as colorless crystals, mp 135.5-136.5 °C (CH_2Cl_2-Et_2O). $[\alpha]_D^{21}$ -131.9° (*c* = 0.90, $CHCl_3$). Ir ν (KBr) : 1669, 1335, 1046 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 2.41 (3H, s), 2.51 (1H, br d, *J* = 20 Hz), 3.06 (1H, br d, *J* = 20 Hz), 5.05 (1H, br d, *J* = 8 Hz), 6.81 (1H, br d, *J* = 8 Hz), 7.3-7.6 (9H, m), 7.71 (1H, s). Ms (EI) *m/z* (%): 323 (M^+, 0.2), 307 (16), 306 (58), 139 (3.5), 105 (100), 91 (13), 77 (100). *Anal.* Calcd for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.30; N, 4.33; S, 9.91. Found: C, 70.52; H, 5.30; N, 4.33; S, 9.89.

General Procedure for the Preparation of 1-Substituted 1,4-Dihydropyridines (1). To a solution of **4** (81 mg, 0.25 mmol) in dry THF (10 ml) were added HMPA (220 μl, 1.25 mmol) and MeLi (1.10 M in THF, 500 μl, 0.55 mmol) under an argon atmosphere at 0°C. After stirring was continued for 30 min in the dark, benzyl bromide (45 μl, 0.38 mmol) was added dropwise to this solution, and stirring was continued for 90 min. Water (2 ml) was added and the solution was stirred for 10 min and then concentrated. The residue was diluted with CH_2Cl_2 and the organic layer was washed with water and brine and dried over Na_2SO_4. Filtration and concentration gave the crude product, which was purified by SiO_2 column chromatography [AcOEt-hexane (1:1)] to give **1c** (70 mg, 90%) as a white solid.
Physical properties (tlc, mp, $[\alpha]_D$, ^{1}H-nmr and ir) of compounds (**1b**) and (**1c**) were identical with those of authentic samples prepared by the previous method.[1] Chemical yields of **1** are summarized in Table 2, and spectral data of **1a** and **1d-1h** are shown below.

(S_S)-3-(*p*-Tolylsulfinyl)-1,4-dihydropyridine (1a). Colorless crystals, mp 133-135°C (Et_2O). $[\alpha]_D^{21}$ +392.9° (*c* = 0.47, $CHCl_3$). Ir ν (KBr) : 3262, 3111, 2990, 2827, 1673, 1617, 1492, 1167, 1082, 1001 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 2.41(3H, s), 2.44 (1H, br d, *J* = 18 Hz), 3.10 (1H, br d, *J* = 18 Hz), 4.56 (1H, m), 5.41 (1H, br), 5.85 (1H, m), 6.87 (1H, d, *J* = 5 Hz), 7.30, 7.50 (4H, AA'BB', *J* = 18 Hz). Ms (CI) *m/z* (%) : 220 (MH^+, 100), 218 (43.6), 202 (37.7), 80 (71.8). High ms Calcd for $C_{12}H_{13}NOS$: 219.0715. Found: 219.0699.

(S_S)-1-Methoxymethyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine (1d). A colorless oil. $[\alpha]_D^{20}$ +145.9° (*c* = 1.91, $CHCl_3$). Ir ν (KBr) : 3051, 3026, 2925, 2828, 1676, 1607, 1492, 1444, 1399, 1304, 1282, 1211, 1192, 1177, 1093, 1038 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 2.41 (3H, s), 2.44 (1H, dd, *J* = 19, 3 Hz), 3.07 (1H, dd, *J* = 19, 2 Hz), 3.33 (3H, s), 4.44 (2H, s), 4.65 (1H, ddd, *J* = 8, 3, 2 Hz), 5.84 (1H, d, *J* = 8 Hz), 6.85 (1H, s), 7.30, 7.48 (4H, AA'BB', *J* = 8 Hz). Ms (EI) *m/z* (%) : 263 (M^+, 2.6), 247 (20.0), 246 (100), 232 (11.3), 139 (18.9), 91 (27.1). High ms Calcd for $C_{14}H_{17}NO_2S$: 263.0978. Found: 263.0961.

(S_S)-1-(2-Methoxyethoxymethyl)-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine (1e). Colorless crystals, mp 50-52°C (AcOEt-*n*-hexane). $[\alpha]_D^{20}$ +182.5° (*c* = 0.89, $CHCl_3$). Ir ν (KBr) : 3052, 2924, 2828, 1676,

1607, 1492, 1452, 1400, 1303, 1271, 1208, 1130, 1090, 1035 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 2.41 (3H, s), 2.42 (1H, dd, *J* = 19, 1 Hz), 3.07 (1H, dd, *J* = 19, 3 Hz), 3.40 (3H, s), 3.55-3.65 (4H, m), 4.57 (2H, s), 4.65 (1H, ddd, *J* = 8, 3, 1 Hz), 5.86 (1H, d, *J* = 8 Hz), 6.85 (1H, s), 7.30, 7.48 (4H, AA'BB', *J* = 8 Hz). Ms (EI) *m/z* (%) : 307 (M^+, 0.9), 291 (13.2), 290 (57.1), 232 (11.5), 89 (60.7). High ms Calcd for $C_{16}H_{21}NO_3S$: 307.1240. Found: 307.1240.

***t*-Butyl (*S*S)-3-(*p*-Tolylsulfinyl)-1,4-dihydropyridine-1-carboxylate (1f).** A colorless oil. $[\alpha]_D^{22}$ -54.5° (*c* = 0.14, $CHCl_3$). Ir ν (KBr) : 2979, 1718, 1684, 1628, 1457, 1361, 1336, 1164, 1136, 1082, 1028 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 1.54 (9H, s), 2.37 (1H, br d, *J* = 20 Hz), 2.41 (3H, s), 3.00 (1H, br d, *J* = 20 Hz), 4.92 (1H, br), 6.67 (1H, br), 7.31, 7.50 (4H, AA'BB', *J* = 8 Hz), 7.68 (1H, br). Ms (EI) *m/z* (%) : 319 (M^+, 0.2), 303 (1.8), 302 (7.8), 246 (45.3), 218 (18.6), 139 (15.4). High ms Calcd for $C_{17}H_{21}NO_3S$: 319.1240. Found: 319.1223.

2-Trimethylsilylethyl (*S*S)-3-(*p*-Tolylsulfinyl)-1,4-dihydropyridine-1-carboxylate (1g). Colorless crystals, mp 34.5-36°C (*n*-hexane). $[\alpha]_D^{20}$ - 63.5° (*c* = 0.32, $CHCl_3$). Ir ν (KBr) : 2954, 1727, 1685, 1630, 1394, 1334, 1310, 1275, 1251, 1173, 1127, 1083, 1048 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 0.07 (9H, s), 1.09 (2H, t, *J* = 9 Hz), 2.38 (1H, d, *J* = 18 Hz), 2.40 (3H, s), 2.98 (1H, d, *J* = 18 Hz), 4.34 (2H, t, *J* = 9 Hz), 4.94 (1H, br), 6.69 (1H, br), 7.31, 7.48 (4H, AA'BB', *J* = 8 Hz), 7.64 (1H, br). Ms (EI) *m/z* (%) : 363 (M^+, 0.3), 347 (6.1), 346 (16.8), 290 (61.0), 139 (15.4), 101 (100). High ms Calcd for $C_{18}H_{25}NO_3SSi$: 363.1325. Found: 363.1343.

Allyl (*S*S)-3-(*p*-Tolylsulfinyl)-1,4-dihydropyridine-1-carboxylate (1h). A colorless oil. $[\alpha]_D^{19}$ - 62.2° (*c* = 0.17, $CHCl_3$). Ir ν (KBr) : 2952, 1730, 1685, 1630, 1394, 1376, 1333, 1312, 1274, 1174, 1132, 1083, 1046 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 2.41 (1H, br), 2.41 (3H, s), 2.95 (1H, br), 4.75 (2H, d, *J* = 6 Hz), 4.97 (1H, br), 5.33 (1H, d, *J* = 11 Hz), 5.37 (1H, d, *J* = 19 Hz), 5.96 (1H, m), 6.72 (1H, br), 7.32, 7.49 (4H, AA'BB', *J* = 8 Hz), 7.65 (1H, br). Ms (EI) *m/z* (%) : 303 (M^+, 0.5), 287 (23.6), 286 (100), 246 (4.3), 139 (19.2), 91 (21.9). High ms Calcd for $C_{16}H_{17}NO_3S$: 303.0927. Found: 303.0922.

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