Asymmetric Synthesis of Pyridylethanols and Amino Alcohols by Enantioselective Reduction with Lithium Borohydride Modified with *N,N'*-Dibenzoylcystine

Kenso Soai,* Seiji Niwa, and Takashi Kobayashi

Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Shinjuku, Tokyo 162, Japan

Optically active 1-pyridylethanols and β- and γ-amino alcohols are obtained in high enantiomeric excess from the enantioselective reduction of acetylpyridines and amino ketones using lithium borohydride, *N,N'*-dibenzoylcystine, and ethanol.

Optically active 1-pyridylethanols can be employed in the synthesis of optically active, naturally occurring, or pharmaceutically active compounds such as *allo*-heteroyohimbine[1] and (*S*)-naproxen.[2] In order to synthesise these compounds, 1-(3- and 4-pyridyl)ethanols of (*R*)-configuration are required respectively. However, only the (*S*)-isomers of 1-(3- and 4-pyridyl)ethanols are obtained on microbial [*Sporotrichum exile* (QM-1250),[1] or *Cryptococcus macerans*[3]] reduction of the corresponding 3- and 4-acetylpyridines. Therefore a carefully controlled inversion sequence (taking three steps) is required.[1] In reduction of acetylpyridines by chemical methods the degree of asymmetric induction is low to moderate.[4] Reduction with *B*-3-pinanyl-9-borabicyclo-[3.3.1]nonane requires elevated pressure (6000 atm).[4d]

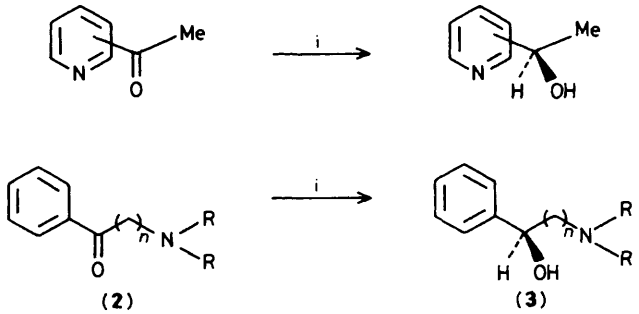
Optically-active amino alcohols also show pharmacological activity and can be employed in asymmetric synthesis of optically active compounds.[5] Their synthesis is limited to the enantioselective reduction of amino ketones with chiral metal hydrides.[6]

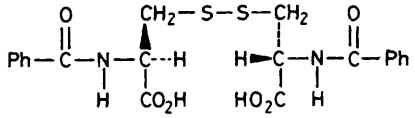
We report an enantioselective reduction which is effective

Table 1. Enantioselective reduction of (**2**) to (**3**) with $LiBH_4$–(*R*,*R'*)-(**1**)–EtOH.

Entry	Compound (**2**)	Compound (**3**) $[\alpha]_D$ (*c*, solvent)	Yield (%)	% E.e.	Configuration
1	4-Acetylpyridine	$[\alpha]_D^{23}$ +31.11° (2.0, EtOH)	72	79[a]	*R*
2	3-Acetylpyridine	$[\alpha]_D^{25}$ +35.06° (0.88, MeOH)	73	87[b](84)[c]	*R*
3	2-Acetylpyridine	$[\alpha]_D^{26}$ +31.68° (1.87, EtOH)	58	56[a]	*R*
4	*n* = 1, R = Me	$[\alpha]_D^{22}$ +35.58° (4.01, MeOH)	70	85[d]	*S*
5	*n* = 1, R = $CH_2[CH_2]_3CH_2$	$[\alpha]_D^{20}$ +39.54° (1.43, MeOH)	73	82[e]	*S*
6	*n* = 1, R = $CH_2CH_2OCH_2CH_2$	$[\alpha]_D^{26}$ +41.83° (5.07, MeOH)	69	89[f]	*S*
7	*n* = 2, R = $CH_2[CH_2]_3CH_2$	$[\alpha]_D^{24}$ +20.68° (2.15, MeOH)	58	71[g]	*R*

[a] Based on the maximum values of optical rotations, $[\alpha]_D$ −39.4° (*c* 2.0, EtOH) for (*S*)-1-(4-pyridyl)ethanol and $[\alpha]_D$ −56.6° (*c* 6.3, EtOH) for (*S*)-1-(2-pyridyl)ethanol, respectively (ref. 9). [b] Based on the maximum value $[\alpha]_D$ −40.2° (*c* 0.87, MeOH) (ref. 10). [c] Determined by g.l.c. analysis of the corresponding (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ester (ref. 8). Conditions: poly(ethylene glycol) (PEG) 20 M, 25 m capillary column, column temp. 190 °C, flame ionisation detector. Retention time 21 min for the minor diastereoisomer, 23 min for the major diastereoisomer. [d] Based on the maximum value $[\alpha]_D$ 42.1° (MeOH). See ref. 4b. [e] Based on the value of $[\alpha]_D$ +28.9° (MeOH) for 60% e.e. See ref. 4b. [f] Based on the value of $[\alpha]_D$ +33.3° (MeOH) for 71% e.e. See ref. 4b. [g] Based on the maximum value $[\alpha]_D$ −29.3° (*c* 1.9, MeOH) (ref. 11).





(*R*,*R'*)-(**1**)

Reagents: i, (*R*,*R'*)-(**1**), $LiBH_4$, EtOH, tetrahydrofuran (THF).

with both acetylpyridines and α- and β-amino ketones using chiral lithium borohydride ($LiBH_4$) modified with *N*,*N'*-dibenzoylcystine (**1**) and ethanol. When 3-acetylpyridine was reduced with $LiBH_4$–(*R*,*R'*)-(**1**)[7]–EtOH, (*R*)-1-(3-pyridyl)-ethanol was obtained in 87% enantiomeric excess (e.e.) [84% e.e. by g.l.c. analysis of the methoxy(trifluoromethyl)phenylacetyl (MTPA) ester[8]] (Table 1, entry 2).† Unlike the microbial reductions,[1,3] the present configuration is suitable for the synthesis of the above mentioned compounds.[1,2] No reduction of the pyridine ring was observed under these reaction conditions.‡

Additionally, α-amino ketones were reduced to (*S*)-β-amino alcohols (entries 4—6), and a β-amino ketone was reduced to (*R*)-γ-amino alcohol (entry 7) in high e.e. Although the configuration of the products varies, in all cases the hydride attacks the carbonyl group of (**2**) from the same side.

Using this simple method, both optically active 1-pyridyl-ethanols and β- and γ-amino alcohols can be obtained in high e.e.

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† To a mixture of (*R*,*R'*)-(**1**) (538 mg, 1.2 mmol) and EtOH (1.6 mmol, 1.60 ml of 1.0 M THF solution) in THF (8 ml), $LiBH_4$ (3.6 mmol, 3.40 ml of 1.06 M THF solution) was added under an argon atmosphere. After refluxing for 30 min, the mixture was cooled to −78 °C and 3-acetylpyridine (121 mg, 1.0 mmol) in THF (2 ml) was added over a period of 10 min. The mixture was stirred for 5 h at −78 °C, then the reaction was quenched by the addition of 1 M HCl (5 ml). The mixture was made alkaline with 5% aqueous $NaHCO_3$, and was extracted with Et_2O. The organic extract was washed with 5% aqueous $NaHCO_3$ and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified on alumina t.l.c. (developing solvent AcOEt/MeOH 40/1, v/v). (*R*)-1-(3-Pyridyl)-ethanol was obtained in 73% yield (90 mg).

‡ Satisfactory results were obtained from n.m.r., i.r. spectroscopy and high resolution mass spectrometric analyses.

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