Asymmetric Reduction of Prochiral Cyclic Imines to Alkaloid Derivatives by Novel Asymmetric Reducing Reagent in THF or under Solid-State Conditions

A. R. Hajipour* and M. Hantehzadeh

Pharmaceutical Research Laboratory, College of Chemistry, Isfahan University of Technology, Isfahan, IR, Iran

Received February 12, 1999

Asymmetric reductions of prochiral cyclic imines were studied using chiral nonracemic sodium acyloxy borohydride **2**. The chiral nonracemic reducing agent **2** has been easily prepared by the reaction of $NaBH_4$ with *N*,*N*-phthaloyl amino acid **1** in THF. The reagent reduces the prochiral cyclic imines **3** and **5** to the alkaloid derivatives **4** and **6** in good enantioselectivity (65−75% ee). The reduction of prochiral cyclic imines with the reagent in the presence of $ZnCl_2$ or under solid-state conditions showed higher enantioselectivity (83−100% ee).

Introduction

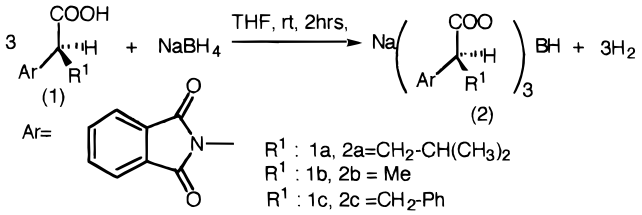
As part of our continued effort to synthesize various biologically important alkaloids,[1−3] our attention has been focused on the development of efficient reducing agents for reducing cyclic imines to the corresponding chiral nonracemic alkaloid derivatives. Chiral nonracemic asymmetric reducing reagents have been used for reduction of prochiral ketones to the corresponding enantiomerically enriched alcohols[4] and prochiral cyclic imines to enantiomerically enriched alkaloids; however, the enantioselectivity is low, and in some cases the using catalyst is expensive.[5]

Results and Discussion

For this purpose, we decided to prepare sodium *N*,*N*-phthaloyl]amino acyloxy borohydride **2**, which has been prepared from the reaction of $NaBH_4$ and *N*,*N*-phthaloylamino acid **1**[6] in THF solution (Scheme 1).

Addition of reducing agent **2** to prochiral cyclic imines **3** or **5** gave the alkaloids **4** or **6** in 75−80% yield. The enantiomeric excess of **4** or **6** was determined to be 65−75% from ^{1}H NMR chiral nonracemic shift studies using (−)-(*R*)-*N*-(3,5-dinitrobenzoyl)-α-phenylethylamine as a chiral shift reagent[3] and comparing the optical rotation of **4** or **6** with known compounds.[5,7−11] To determine the enantiomeric excess of the product, we mixed it with 1 equiv of chiral shift reagent in an NMR tube. The ^{1}H NMR spectrum of pure **4b** showed a singlet (δ 4.96 (s, 1 H)). In the presence of the chiral shift reagent, peaks for the major *S* enantiomer and the minor *R* enantiomer could be detected in a ratio of 82.5:17.5. To explain the higher stereoselectivity attained through these reactions detailed above, we assume that the reaction proceeds preferentially via transition state A. The results led us to investigate the steric bulkiness of R^1 group in *N*,*N*-phthaloylamino acyloxy borohydride **2**, which may control the reduction course effectively and improve the enantioselectivity for the reducing agent **2a** and **3a**−**d** or **5a**−**d**. In the transition state, the *si*-face (transition B) has higher steric hindrance than the *re*-face (transition state A) (Figure 1). Addition of hydride to the borane-chelated form (transition state A and B) from the least sterically demanding face (i.e., *re*-face) of the cyclic imines accounted for the stereochemical outcome of the reduction of these compounds.

Scheme 1



The addition of **2** to **3** or **5** in the presence of $ZnCl_2$ showed higher enantioselectivity (72−80% ee) (Scheme 2, Tables 1 and 2). Consequently, when **3** or **5** was treated with **2a**, the enantioselectivity obtained was higher with $ZnCl_2$ (Tables 1−3). In the transition states C and D, the zinc atom coordinates to the nitrogen atoms of cyclic imine and oxygen of the phthaloyl groups, and the *si*-face (transition D) has higher steric hindrance than the

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10.1021/jo990267k CCC: $18.00
Published on Web 10/22/1999

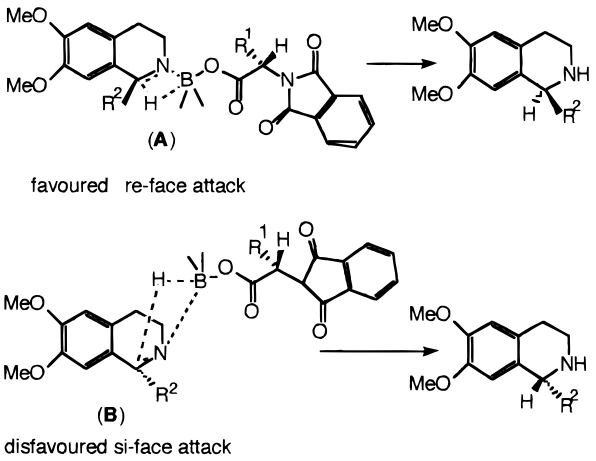

Figure 1.

Scheme 2

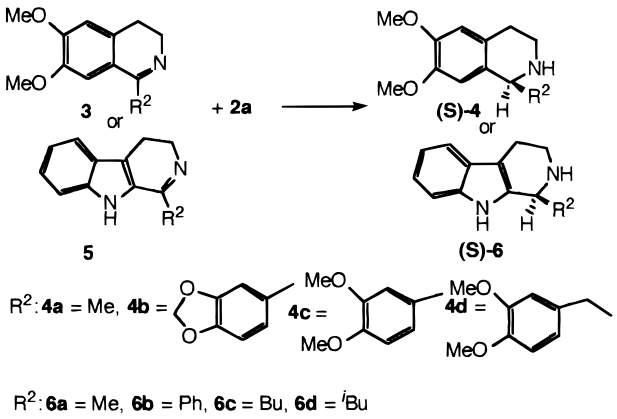

Table 1. Asymmetric Reduction of 3 or 5 to 4 or 6 with Reducing Agent 2a

entry	product	reaction time (h)	$[\alpha]^{25}_D$ (c 1, $CHCl_3$)	chemical yield (%)	ee (%)
1	**4a**	8	−44.6	79	75
2	**4b**	6	−15.0	77	65
3	**4c**	7	−23.8	76	70
4	**4d**	8	+25.2[a]	80	68
5	**6a**	5	−36.9	78	71
6	**6b**	6	−11.3	79	69
7	**6c**	7	−59.8	83	74
8	**6d**	7	−57.5	78	72

[a] $[\alpha]^{25}_D$ (c 1, H_2O).

Table 2. Asymmetric Reduction of 3 or 5 to 4 or 6 with Reducing Agent 2a in the Presence of $ZnCl_2$

entry	product	reaction time (h)	$[\alpha]^{25}_D$ (c 1, $CHCl_3$)	chemical yield (%)	ee (%)
1	**4a**	8	−47.6	72	80
2	**4b**	6	−16.6	71	72
3	**4c**	7	−26.5	72	78
4	**4d**	8	+27.4[a]	80	74
5	**6a**	5	−41.1	70	79
6	**6b**	6	−12.3	67	75
7	**6c**	7	−64.6	75	80
8	**6d**	7	−62.3	79	78

[a] $[\alpha]_D^{25}$ (c 1, H_2O).

re-face (transition C) (Figure 2). This is in accordance with the finding for the reduction of β-keto sulfoxides in the presence of $ZnCl_2$.[12]

The stereochemistry of **4** and **6** is based on a comparison of the [α] of these compounds with those of related

Table 3. Asymmetric Reduction of 5a to 6a with Reducing Agents 2

reducing agent **2**	product	reaction time (h)	$[\alpha]^{25}_D$ (c 1, $CHCl_3$)	chemical yield (%)	ee (%)
2a	**6a**	5	−42.2	78	71
2b	**6a**	4	−35.7	82	60
2c	**6a**	4	−36.9	80	62

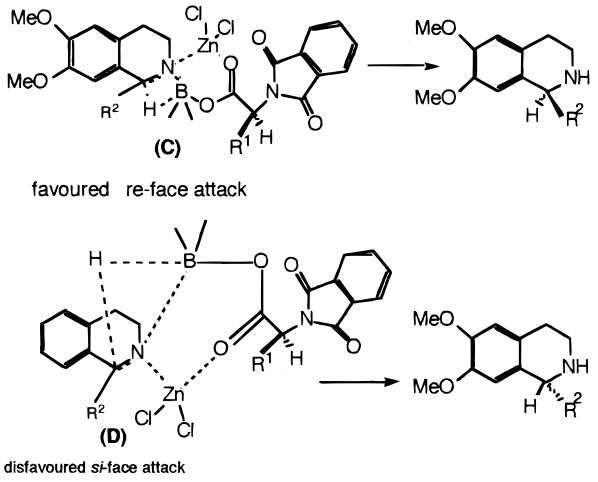

Figure 2.

Table 4. Effect of Solvents in the Asymmetric Reduction of 5a to 6a with Reducing Agents 2a

solvent	reaction time (h)	$[\alpha]^{25}_D$ (c 1, $CHCl_3$)	chemical yield (%)	optical yield (%)
THF	5	−42.2	78	71
Et_2O	12	−30.9	45	52
CH_2Cl_2	144	−33.3	50	56
DME	123	−34.5	55	58
$CHCl_2CHCl_2$	40	−36.9	65	62

alkaloids[5,7−11] and is in accordance with those expected from the reduction of imines **3** and **5** on the favored conformation shown in transitions state A (Figure 1) or transition state C (Figure 2). Satisfactory enantioselectivities were obtained by using reducing agent **2a**. The results obtained with **2b** and **2c** showed a lowering in the enantioselectivities. These results may be explained by less steric hindrance for the **2b** and **2c** in the transition state (B or C) (Table 3).

The effect of solvents on this asymmetric reduction was thus examined by the use of reducing agent **2a** in the absence of $ZnCl_2$. The imine **5a** was reduced with **2a** at ambient temperature in various solvents. THF solvent afforded a better chemical and enantiomeric purity of **6a** in a shorter reaction time (Table 4). One might surmise that for a reaction mechanism that requires coordination (N to B) a coordinating solvent like THF might interfere with the reaction (unlike a less coordinating solvent like methylene chloride).

In recent years, organic reactions on solid supports[13] under solvent-free conditions have attracted attention.[14]

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Table 5. Asymmetric Reduction of 3 or 5 to 4 or 6 with Reducing Agent 2a in Solid State Conditions

entry	product	reaction time (min)	$[\alpha]^{25}_D$ (*c* 1, $CHCl_3$)	chemica yield (%)	ee (%)
1	**4a**	60	−59.5	90	100
2	**4b**	55	−21.4	80	93
3	**4c**	60	−32.3	81	95
4	**4d**	50	+36.3[a]	83	98
5	**6a**	50	−51.0	90	98
6	**6b**	60	−15.4	89	94
7	**6c**	50	−80.8	93	100
8	**6d**	50	−79.1	90	99

[a] $[\alpha]_D^{25}$ (*c* 1, H_2O.

The advantage of these methods over conventional homogeneous reactions is that they provide greater selectivity, enhanced reaction rates, cleaner products, and manipulative simplicity. We anticipated that the reduction of the prochiral cyclic imine **3** or **5** in the solid state under solvent-free conditions may be stereoselective. We repeated the above reduction reaction in the solid state under solvent-free conditions and have found that the alkaloids **4** or **6** were formed in higher chemical yield and enantiomeric purity in less than 60 min. The process involves a simple mixing of supported **2a** on alumina[15] with an appropriate prochiral cyclic imine in a mortar, followed by grinding the mixture for the time specified in Table 5. The chemical yields and enantioselectivity of the reactions are excellent (80−92%, ee 93−100%), and the reaction times are exceedingly short (50−60 min).

In conclusion, because these cyclic imines are easily accessible by the Bishler−Napieraski reaction,[16] the synthesis of the new chiral nonracemic reducing agent **2** provides a very effective route to various enantiomerically enriched alkaloids. Moreover, the reagents are quite inexpensive, since *N,N*-phthaloylamino acid **1** can be recovered in nearly quantitative yield after the reduction.

Experimental Section

General Methods. The *N,N*-phthaloyl-(*S*)-amino acid **1** was prepared from (S)-amino acid and phthalic anhydride by a known method.[6] All products were identified by comparison with an authentic sample (IR, NMR, mp). Elemental analysis was performed by the Research Institute of Petroleum Industry, Tehran, IR, Iran. The ^{1}H NMR spectra were measured in $CDCl_3$ unless otherwise stated, relative to TMS (0.00 ppm).

Synthesis of Chiral Nonracemic Reducing Agent 2. General Method. (*S*)-*N,N*-phthaloylamino acid **1** (6 mmol) in THF (10 mL) was added to a suspension of $NaBH_4$ (76 mg, 2 mmol) in THF (15 mL) at room temperature. After vigorous hydrogen evolution ceased, the mixture was stirred at ambient temperature for 10 h and then concentrated under reduced pressure. The residue was digested with *n*-hexane and filtered to give **2**.

Sodium tris[*(S)-N,N*-Phthaloylleucine]borohydride: white powder (1.58 g, 96%); mp 193−194 °C dec; $[\alpha]^{25}_D$ −28.5 (*c* 1.4. THF). Anal. Calcd for $C_{39}H_{37}BNaN_3O_{12}$: C, 60.56; H, 4.82; N, 5.48. Found: C, 60.40; H, 4.90; N, 5.40.

Sodium tris[*(S)-N,N*-phthaloylalanine]borohydride: white powder (1.27 g, 94%); mp 178−191 °C dec; $[\alpha]^{25}_D$ −26.4 (*c* 1.2. THF). Anal. Calcd for $C_{33}H_{25}BNaN_3O_{12}$: C, 58.40; H, 3.72; N, 6.19. Found: C, 58.30; H, 3.90; N, 6.10.

Sodium tris[*(S)-N,N*-phthaloylphenylalanine]borohydride: white powder (1.80 g, 98%); mp 223−225 °C dec; $[\alpha]^{25}_D$ −232.5 (*c* 1.1. THF). Anal. Calcd for $C_{51}H_{37}BNaN_3O_{12}$: C, 66.75; H, 4.06; N, 4.58. Found: C, 66.70; H, 4.20; N, 4.50.

Asymmetric Reduction of Cyclic Imines 3 and 5 to 4 and 6 with 2a. General Procedure: Method A. A solution of cyclic imine (1.0 mmol) in THF (10 mL) was added to a stirred solution of **2a** (0.45 g, 1.2 mmol), and the whole was stirred at ambient temperature for the time specified in Table 1. After concentration, the residue was treated with 5% aqueous HCl (20 mL, 50 °C for 1 h) and then made basic with $KHCO_3$. The reaction mixture was extracted with ethyl acetate (2 × 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc−MeOH, 9:1) to afford **4** or **6** (Table 1).

Method B. The procedure is as described except 1.2 equiv of dried $ZnCl_2$ was added. The yield and ee of the products are listed in Table 2.

Method C. A mortar was charged with cyclic imine (1 mmol), alumina (0.3 g) and **2a** (0.45 g, 1.2 mmol). The reaction mixture was ground with a pestle in the mortar. When TLC showed no remaining cyclic imine, the reaction mixture was poured into a mixture of ethyl acetate (20 mL) and 1 N HCl (5 mL) and made basic with $KHCO_3$. The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc−MeOH, 9:1) to afford **4** or **6** (Table 5).

(*S*)-(−)-Salsolidine 4a. Method A: slightly yellowish oil; $[\alpha]^{25}_D$ −44.6 (*c* 2.1, $CHCl_3$) (ee 75%) [lit.[7] $[\alpha]^{25}_D$ −59.5 (*c* 4.39, EtOH)]; IR (Nujol) 3552 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 6.62 (s, 1 H, ArH), 6.57 (s, 1 H, ArH), 4.07 (q, 1 H, *J* = 6.6 Hz), 3.84 (s, 6 H, 2xOMe), 3.2 (t, 4 H), 2.25 (s, 1 H, NH, exchange with D_2O), 1.45 (d, 3 H, *J* = 6.6 Hz, Me); Ms *m/z* 208 (56, M^+H^+). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.50; H, 8.30; N, 6.80. Found: C, 69.40; H, 8.50; N, 6.60.

(*S*)-(−)-Norcryptostyline I 4b. Method A: mp 117−119 °C; $[\alpha]^{25}_D$ −15.0 (*c* 1.3, $CHCl_3$) (ee 65%) [lit.[8] mp 122−123 °C; $[\alpha]^{25}_D$ −23.0 (*c* 1.0, $CHCl_3$)]; IR (Nujol) 3556 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 6.59−6.20 (5 H, ArH), 5.90 (s, 2 H, OCH_2O), 4.96 (s, 1 H), 3.85 (s, 3 H, OMe), 3.65 (s, 3 H, OMe), 3.25 (t, 4 H), 2.10 (s, 1 H, NH, exchange with D_2O); MS *m/z* 313 (64, M^+H^+).

(*S*)-(−)-Norcryptostyline II 4c. Method A: mp 108−111 °C; $[\alpha]^{25}_D$ −23.8 (*c* 1.1, $CHCl_3$) (ee 70%) [lit.[7] mp 114−115 °C; $[\alpha]^{25}_D$ −34.0 (*c* 1.0, $CHCl_3$)]; IR (Nujol) 3554 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 6.55 (s, 1 H, ArH), 6.42 (s, 1 H, ArH), 4.99 (s, 1 H), 3.89 (s, 6 H, 2 × OMe), 3.68 (s, 6 H, 2 × OMe),3.20 (t, 4 H), 2.45 (s, 1 H, NH, exchange with D_2O); MS *m/z* 330 (75, M^+H^+) 328, and 192.

(*S*)-(+)-Norlaudanosine 4d Hydrochloride. Method A: colorless prisms; mp 210−212 °C; $[\alpha]^{25}_D$ +25.2 (*c* 1.0, H_2O) (ee 68%) [lit.[9,10] mp 215 °C; $[\alpha]^{25}_D$ +37.0 (*c* 1.0, H_2O)]; IR (Nujol) 3100 cm^{-1}; ^{1}H NMR δ (D_2O) 7.90−6.70 (m, 4 H, ArH), 6.39 (s, 1 H, ArH), 5.47 (dd, 1 H, *J* = 3.2, 6.0 Hz), 4.80 (dd, 1 H, *J* = 3.6, 13.6), 4.68 (dd, 1 H, *J* = 6.0, 13.6), 3.88 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 3.80 (s, 6 H, 2 × OMe), 2.85 (t, 4 H).

1-Methyltetrahydro-*β*-carboline 6a. Method A: semisolid; $[\alpha]^{25}_D$ −36.9 (*c* 0.98, $CHCl_3$) (ee 71%) [lit.[5] $[\alpha]^{25}_D$ −52 (*c* 1.0, EtOH)]; IR (Nujol) 3325 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 7.75 (s, 1 H, NH), 7.48 (d, 1H, *J* = 7.6 Hz, ArH), 7.31 (dd, 1 H, *J* = 1.0, 8.0 Hz, ArH), 7.20 (dt, 1 H, *J* = 1.2, 8.0 Hz, ArH), 7.10 (dt, *J* = 1.0, 8.0 Hz, ArH), 4.20 (q, 1H, *J* = 6.8), 2.92 (t, 2H, *J* = 5.6, CH_2), 2.72 (t, 2 H, *J* = 5.6, CH_2). 1.58 (s, 1 H, NH), 1.46 (d, 3 H, *J* = 6.8, Me); MS *m/z* 187 (45, M^+H^+) 172 (100).

1-Phenyltetrahydro-*β*-carboline 6b. Method A: semisolid; $[\alpha]^{25}_D$ −11.3 (*c* 0.90, $CHCl_3$) (ee 69%) [lit.[5] $[\alpha]^{25}_D$ −16.4 (*c* 0.38, EtOH)]; IR (Nujol) 3330 cm^{-1};, ^{1}H NMR δ ($CDCl_3$) 7.75−6.85 (m, 9 H, ArH), 5.28 (s, 1 H, NH), 5.10 (s, 1 H), 3.25 (t, 2H, *J* = 5.4, CH_2), 2.90 (t, 2H, *J* = 5.4, CH_2), (1.73 (s, 1 H, NH); MS *m/z* 249 (100, M^+H^+).

1-Butyltetrahydro-*β*-carboline 6c. Method A: oil; $[\alpha]^{25}_D$ −59.8 (*c* 0.65, $CHCl_3$) (ee 74%) [lit.[5] $[\alpha]^{25}_D$ −80.86 (c 0.55, EtOH)]; IR (Nujol) 3345 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 7.70 (s, 1 H, NH), 7.45 (d, 1H, *J* = 7.6 Hz, ArH), 7.36 (dt, 1 H, *J* = 1.0, 8.0 Hz, ArH), 7.28 (dt, 1 H, *J* = 1.0, 8.0 Hz, ArH), 7.14 (d, *J* = 7.6

(15) Alumina, type 507 C neutral: 100−125 mesh, Fluka.
(16) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74.

Hz, ArH), 4.10 (dd, 1 H, 5.22. 13.6 Hz), 3.22 (t, 2H, J = 5.4, CH_2),2.78 (t, 2H, J = 5.4, CH_2), 1.88 (m, 2 H), 1.71−131 (m, 6 H). Ms m/z 249 (100, M^+H^+).

1-Isobutyltetrahydro-*β*-carboline 6d. Method A: oil; $[\alpha]^{25}_D$ −57.5 (*c* 0.45, $CHCl_3$) (ee 72%) [lit.[5] $[\alpha]^{25}_D$ −79.8 (*c* 1.01, MeOH)]; IR (Nujol) 3345 cm^{-1}; ^1H NMR δ ($CDCl_3$) 7.78 (s, 1 H, NH), 7.49 (d, 1H, J = 7.8 Hz, ArH), 7.36 (dt, 1 H, J = 1.2, 8.6 Hz, ArH), 7.28 (dt, 1 H, J = 1.2, 8.6 Hz, ArH), 7.14 (d, J = 7.8 Hz, ArH), 4.12 (dd, 1 H, 5.60. 13.8 Hz), 3.18 (t, 2H, J = 5.8, CH_2), 2.80 (t, 2H, J = 5.8, CH_2), 1.98 (m, 2 H), 1.82 (s, 1 H, NH), 1.63 (m, 1 H), 1.00 (d, 6 H, J = 6.3 Hz); M**s** m/z 229 (100, M^+H^+).

Acknowledgment. Partial support of this work by the Isfahan University of Technology Research Council is gratefully acknowledged.

JO990267K