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A Simple Diastereoselective Synthesis of Chiral Nonracemic Aliphatic Amines

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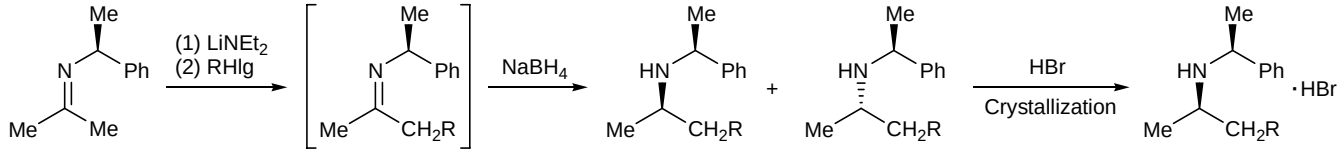
Abstract—An efficient procedure has been developed for the diastereoselective synthesis of chiral aliphatic amines (diastereoisomeric excess >96%) from (1*S*)-*N*-(1-methylethylidene)-1-phenylethylamine, i.e., Schiff base derived from the simplest ketone (acetone) and (1*S*)-1-phenylethylamine. The procedure includes successive lithiation, alkylation, and reduction and is characterized by high regioselectivity in the formation of alkylated *syn*-*Z*-imines. Hydride reduction of the prochiral C=N bond in the latter gives mainly optically active aliphatic amines with *R* configuration. All reactions are performed as a one-pot process without isolation of intermediate products.

Enantiomerically pure amines are widely used as chiral auxiliaries for resolution of racemic mixtures in asymmetric synthesis, chiral ligands in metal-complex catalysis, and chiral building blocks in the preparation of synthetic and natural biologically active compounds [1–5].

In the present communication we describe an efficient stereoselective synthesis of chiral aliphatic amines having *R* configuration from (1*S*)-*N*-(1-methylethylidene)-1-phenylethylamine (**I**) which is obtained from the simplest ketone, acetone, and (1*S*)-1-phenylethylamine. The proposed procedure ensures more than 96% diastereoisomeric excess. Metalation of Schiff base **I** with lithium diethylamide in THF at –20°C, followed by alkylation with methyl iodide at –80°C and reduction with 4 equiv of sodium tetrahydridoborate at –80°C in the presence of 40 equiv of isopropyl alcohol, gave a mixture of (R_C,S_N)- and (S_C,S_N)-epimeric amines **IIIa** and **IVa** (the former prevailing, de 79%) through intermediate *syn*-*Z*-imine **IIa**. The entire reaction sequence was performed as a one-pot process, without isolation of intermediate products (Scheme 1). The crude products were treated with concentrated hydrobromic acid in ethanol at pH ~4 to obtain a mixture of the corresponding hydrobromides. The subsequent removal of the solvent, drying of the residue under reduced pressure over P_2O_5 and fused sodium hydroxide, and recrystallization from anhydrous ethanol–diethyl ether gave 48% of hydrobromide **Va** (de 96%). According to the ^{1}H NMR data, the mother liquor contained an inseparable mixture of epimeric hydrobromides at a ratio of 1.3:1 (**IIIa**:**IVa**). The ratio was determined from the intensities of the methyl proton signals, δ 0.99 (**IIIa**) and 0.94 ppm (**IVa**).

The structure of hydrobromides **Va**–**Vd** derived from amines **IIIa**–**IIId** was confirmed by their analytical data and ^{1}H and ^{13}C NMR spectra; their properties are given in Experimental. Diastereoisomeric excess was determined by ^{1}H NMR spectroscopy for the free bases in $CDCl_3$. Optically active amines **IIIb**–**IIId** were obtained with de 68–82%. The correspond-

Scheme 1.



I *Z*-**IIa**–*Z*-**IId** **IIIa**–**IIId** (R_C, S_N) **IVa**–**IVd** (S_C, S_N) **Va**–**Vd**

RHlg = MeI (**a**), EtI (**b**), CH_2=$CHCH_2Br$ (**c**), 4-$MeC_6H_4CH_2I$ (**d**).

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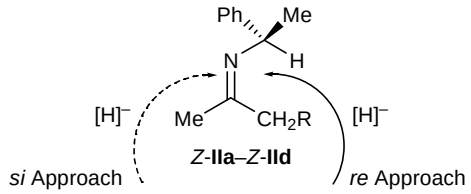
ing diastereoisomerically pure hydrobromides **Vb**–**Vd** (de >98%) were isolated in 31–48% yield. Below are given the compositions of diastereoisomer mixtures **III**/**IV** (according to the ^{1}H NMR data) and chemical shifts of the methyl protons at the new chiral center.

Amine	**IIIa**/**IVa**	**IIIb**/**IVb**	**IIIc**/**IVc**	**IIId**/**IVd**	**IIId**/**IVd**[a]
de, %	79	78	68	82	44
δ_{III}, ppm	0.99	0.99	1.05	1.03	1.03
δ_{IV}, ppm	0.94	0.94	1.01	1.00	1.00

[a] RHlg = 4-Me$C_6H_4CH_2$Cl.

Presumably, the key stereochemical stage in the reaction under study is formation of intermediate *syn*-alkylated imines **IIa**–**IId**. The subsequent hydride reduction of the prochiral C=N bond therein is more favorable from the less sterically shielded *re* side, as shown in Scheme 2. As a result, amines **IIIa**–**IIId** having *R* configuration of the new chiral center are mainly formed.

Scheme 2.



The stereochemical composition of Schiff base **IIa** during alkylation was monitored by ^{13}C NMR spectroscopy at room temperature (the spectra of samples withdrawn from the reaction mixture were recorded as quickly as possible). We found that the *Z* and *E* isomers of **IIa** were formed at a ratio of 3:1 (NCH: δ_C 57.9 and 57.5 ppm, respectively). We believe that an appreciable amount of *E*-**IIa** is formed via *Z*–*E* isomerization at room temperature. This assumption is confirmed by the fact that the reduction under the same conditions (–80°C, 4 equiv of $NaBH_4$, 40 equiv of isopropyl alcohol) of Schiff base **IIa** with a *Z*/*E* isomer ratio of 1:4 (which was obtained by heating **IIa** for 1 h in boiling THF) afforded diastereoisomer **IVa** as the major product but with a diastereoisomeric excess of only 43%.

The above synthetic strategy for the preparation of optically pure (*R*)-amines **IIIa**–**IIId** was selected taking into account highly regioselective formation of *syn*-imines **IIa**–**IId** due to determining role of the *syn* effect in the deprotonation of Schiff bases and α-alkylation of their lithium derivatives [6]. Obviously, the *syn* orientation of the carbanionic center and the *N*-alkyl substituent in the lithiated Schiff base is more favorable from the viewpoint of thermodynamics, and C-alkylation of the lithium derivative is kinetically preferred. The *syn* configuration of lithiated and alkylated imines was confirmed by *ab initio* calculations [7], NMR data [8], and studies on the stereochemistry of α-alkylation of various lithiated Schiff bases [9–11]. For example, Frazer *et al*. [8] performed ^{13}C NMR monitoring of α-alkylation of metalated Schiff bases derived from cycloalkanones and detected only unstable *syn*-alkylated species, while Smith *et al*. [9] observed formation (96%) of a very unstable *syn*-alkylated Schiff base in the methylation of a metalated butyraldehyde imine derivative.

In order to determine the absolute configuration of the whole series of amines **IIIa**–**IIId** we obtained optically active (–)-2-butylamine (**VI**) by removal of the 1-phenylethyl group from amine **IIIa** via hydrogenation over Pd/C. We then compared the signs and magnitudes of the specific rotations of the benzoyl derivatives of (–)-2-butylamine, $[\alpha]_D^{20}$ = –30.2° (*c* = 4.3%, EtOH), and (+)-(2*S*)-2-butylamine, $[\alpha]_D^{20}$ = +31° (*c* = 4–5%, EtOH), whose absolute configuration is known [12]. It is seen that their specific rotations are almost similar in absolute values, but they have opposite signs. This means that (–)-2-butylamine (**VI**) obtained from **IIIa** has *R*-configuration. Likewise, comparison of the specific rotations of (2*R*)-2-butylamine hydrochloride ($[\alpha]_D^{20}$ = +4°, *c* = 2.96%, EtOH [13]) and hydrochloride obtained from **VI** ($[\alpha]_D^{20}$ = +4.1°, *c* = 4.1%, EtOH) indicated identical configurations of the chiral center in these compounds. Therefore, all amines **IIIa**–**IIId** belong to the same *R*-series with respect to the configuration of the new chiral center. It should be noted that the signal from the CH_3 group at that center in the ^{1}H NMR spectra of amines **IIIa**–**IIId** is located appreciably downfield relative to the corresponding signals in the spectra of epimeric amines **IVa**–**IVd**.

The diastereoselectivity in the formation of (R_C,S_N)-amines **IIIa**–**IIId** depends on the nature and amount of the alcohol added at the reduction stage. Below are given the ratios of diastereoisomeric amines **IIIa** and **IVa** formed by reduction of **IIa** with sodium tetrahydridoborate in the presence of different amounts of different alcohols (according to the ^{1}H NMR spectra of the reaction mixtures).

Alcohol	*i*-PrOH	*t*-BuOH	EtOH	EtOH	EtOH	MeOH
Amount, equiv	40	20	40	4	2	60
IIIa:**IVa**	8.5:1	7:1	6:1	3:1	1:1	1:1.25

These data show that the reduction of **IIa** in the presence of *tert*-butyl alcohol (which is sparingly soluble in the reaction mixture at low temperature) and ethanol gives lower diastereoisomeric excess of amine **IIIa** than in the presence of isopropyl alcohol (75 and 71%, respectively). In addition, decrease in the amount of ethanol to 2 equiv leads to complete loss of diastereoselectivity. This pattern may be rationalized on the assumption that the hydride reduction is accompanied by *Z–E* isomerization. Due to high rate of *Z–E* isomerization, amine **IIIa** is formed as minor product in the reduction of Schiff base **IIa** in methanol .

Thus we have proposed a simple and efficient procedure for the synthesis of optically pure aliphatic amines of the *R*-series from acetone and (1*S*)-1-phenylethylamine. Naturally, (1*R*)-1-phenylethylamine should give rise to the corresponding (*S*)-amines. The target products are readily isolated as the corresponding hydrobromides, and the procedure can be used in enlarged syntheses. The proposed procedure complements the existing methods for reductive amination of ketones with the use of 1-phenylethylamine [13–16].

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer. The ^{1}H and ^{13}C NMR spectra were obtained on Varian XL-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) and Bruker WM-300 spectrometers (300 MHz for ^{1}H and 75 MHz for ^{13}C). Thin-layer chromatography was performed on Silufol plates (Kavalier, Czechia). Tetrahydrofuran was distilled over sodium diphenylketyl. (1*S*)-*N*-(1-Methylethylidene)-1-phenylethylamine (**I**) was prepared in 84% yield from acetone and (1*S*)-1-phenylethylamine ($[\alpha]_D^{20}$ = –40.0°, pure grade) according to the procedure described in [17].

[(1*R*)-1-Methylpropyl][(1*S*)-1-phenylethyl]amine hydrobromide (Va). Metalation and alkylation of Schiff base **I** were performed under argon; reactants were added using a syringe through a septum. Compound **I**, 2 g (12.4 mmol), was added to a solution of lithium diethylamide, prepared from 1.36 g (18.6 mmol) of diethylamine in 30 ml of anhydrous THF and 11.6 ml (18.6 mmol) of a 1.6 N solution of butyllithium in hexane by stirring for 10 min at –10°C. The mixture was stirred for 30 min and cooled to –80°C, 2.65 g (18.6 mmol) of methyl iodide was added, the mixture was stirred for 30 min at –80°C, and a suspension of 1.9 g (50 mmol) of sodium tetrahydridoborate in 40 ml of isopropyl alcohol, cooled to –80°C, was added. The mixture was stirred for 30 min at –80°C, the cooling bath was removed, and the mixture was allowed to warm up to room temperature over a period of 1 h under vigorous stirring. The solvent was removed, and the residue was decomposed by carefully adding 6 N hydrochloric acid until hydrogen no longer evolved. The mixture was diluted with 20 ml of water, a 20% solution of sodium hydroxide was added to pH 12, and the mixture was extracted with diethyl ether (2×30 ml). The extracts were combined, dried over anhydrous sodium sulfate, and evaporated. The oily residue was dissolved in 10 ml of ethanol, the solution was cooled to 0°C, and concentrated hydrobromic acid was added to a weakly acidic reaction. The mixture was evaporated, and the residue was dried under reduced pressure over P_2O_5 and fused alkali over a period of 10 h and recrystallized 5 times from anhydrous ethanol–diethyl ether. Yield 1.54 g (48%), mp 200–201°C, $[\alpha]_D^{20}$ = –24° (*c* = 3.2%, EtOH), de 96% (^{1}H NMR data). ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of free base **IIIa**, δ, ppm: 0.82 t (3H, *J* = 7.5 Hz), 0.99 d (3H, *J* = 6.1 Hz), 1.23–1.41 m (2H), 1.33 d (3H, *J* = 6.8 Hz), 2.33 sext (1H, *J* = 6.1 Hz), 3.90 q (1H, *J* = 6.8 Hz), 7.19–7.33 m (5H). ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of free base **IIIa**, δ_C, ppm: 10.4, 19.5, 25.1, 30.6, 51.1, 54.8, 126.4, 126.6, 128.3, 146.1. Found, %: C 55.78; H 8.05; N 5.28. $C_{12}H_{19}N\cdot HBr$. Calculated, %: C 55.82; H 7.81; N 5.42.

[(1*R*)-1-Methylbutyl][(1*S*)-1-phenylethyl]amine hydrobromide (Vb) was synthesized in a similar way from 2 g (12.4 mmol) of compound **I** and 2.91 g (18.6 mmol) of ethyl iodide. The product was recrystallized 4 times from anhydrous ethanol–diethyl ether. Yield 1.42 g (42%), mp 187–188°C, $[\alpha]_D^{20}$ = –14° (*c* = 3.5%, EtOH), de 98% (^{1}H NMR). ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of free base **IIIb**, δ, ppm: 0.81 t (3H, *J* = 7.0 Hz), 0.99 d (3H, *J* = 6.5 Hz), 1.19–1.34 m (4H), 1.33 d (3H, *J* = 6.8 Hz), 2.40 m (1H), 3.90 q (1H, *J* = 6.8 Hz), 7.19–7.33 m (5H). ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of free base **IIIb**, δ_C, ppm: 14.1, 19.1, 20.0, 25.1, 40.4, 49.3, 54.8, 126.4, 126.6, 128.3, 146.1. Found, %: C 57.32; H 8.38; N 5.07. $C_{13}H_{21}N\cdot HBr$. Calculated, %: C 57.36; H 8.15; N 5.15.

[(1*R*)-1-Methyl-4-pentenyl][(1*S*)-1-phenylethyl]-amine hydrobromide (Vc) was synthesized in a similar way from 2 g (12.4 mmol) of compound **I** and 2.25 g (18.6 mmol) of allyl bromide (after addition of allyl bromide, the mixture was stirred for 1 h). The product was recrystallized twice from anhydrous acetone–diethyl ether. Yield 1.10 g (31%), mp 172–175°C, $[\alpha]_D^{20}$ = –24° (*c* = 3.6%, EtOH), de >98%

(^{1}H NMR). ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of free base **IIIc**, δ, ppm: 1.01 d (3H, *J* = 6.3 Hz), 1.28–1.48 m (2H), 1.33 d (3H, *J* = 6.7 Hz), 1.94–2.16 m (2H), 2.42 sext (1H, *J* = 6.3 Hz), 3.90 q (1H, *J* = 6.7 Hz), 4.85–4.97 m (2H), 5.66–5.79 m (1H), 7.19–7.34 m (5H). ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of free base **IIIc**, δ_C, ppm: 20.0, 25.1, 30.4, 37.3, 49.3, 54.8, 114.2, 138.8, 126.5, 126.7, 128.3, 138.8, 146.0. Found, %: C 59.20; H 8.04; N 4.86. $C_{14}H_{21}N \cdot HBr$. Calculated, %: C 59.16; H 7.80; N 4.93.

[(1*R*)-1-Methyl-3-(4-methylphenyl)propyl][(1*S*)-1-phenylethyl]amine hydrobromide (Vd) was synthesized in a similar way from 2 g (12.4 mmol) of compound **I** and 4.32 g (18.6 mmol) of 4-methylbenzyl iodide. The product was recrystallized twice from anhydrous ethanol–ether. Yield 1.98 g (46%), mp 212–213°C, $[\alpha]_D^{20}$ = +4° (*c* = 3.4%, EtOH), de >98% (^{1}H NMR). ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of free amine **IIId**, δ, ppm: 1.04 d (3H, *J* = 6.1 Hz), 1.33 d (3H, *J* = 6.7 Hz), 1.50–1.66 m (2H), 2.28 s (3H), 2.42–2.51 m (2H), 2.60 d.d.d (1H, *J* = 6.0, 10.1, *J* = 13.8 Hz), 3.89 q (1H, *J* = 6.7 Hz), 6.95 and 7.02 (4H, *AB* system, *J* = 8.2 Hz), 7.19–7.32 m (5H). ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of free base **IIId**, δ_C, ppm: 20.2, 20.9, 25.1, 31.9, 39.9, 49.5, 54.9, 126.55, 126.6, 128.1, 128.3, 128.9, 134.9, 139.3, 146.0. Found, %: C 65.64; H 7.68; N 4.13. $C_{19}H_{25}N \cdot HBr$. Calculated, %: C 65.52; H 7.52; N 4.02.

(2*R*)-2-Butylamine hydrochloride (VI). Amine **IIIa**, 0.68 g (3.84 mmol), isolated from hydrobromide amine **Va**, was dissolved in 15 ml of ethanol, 0.220 g of 10% Pd/C was added, and the mixture was hydrogenated for 24 h at room temperature under normal pressure. The mixture was acidified to pH 4–5 with a saturated solution of HCl in methanol, the catalyst was filtered off, the filtrate was evaporated, and the residue was dried under reduced pressure over P_2O_5 and fused sodium hydroxide. The product was recrystallized twice from anhydrous ethanol–diethyl ether. Yield 0.310 g (74%), mp 150–151°C, $[\alpha]_D^{20}$ = +4.1° (*c* = 4.1%, EtOH), de 97%. ^{1}H NMR spectrum (DMSO-d_6, 400 MHz), δ, ppm: 0.89 t (3H, *J* = 7.3 Hz), 1.17 d (3H, *J* = 6.4 Hz), 1.45 m (1H), 1.63 m (1H), 3.05 sext (1H, *J* = 6.7 Hz), 7.99 br.s (3H). Found, %: C 43.87; H 11.33; N 12.65. $C_4H_{11}N \cdot HCl$. Calculated, %: C 43.84; H 11.04; N 12.78. Benzoyl derivative: mp 95–96°C, $[\alpha]_D^{20}$ = –30.2° (*c* = 4.3%, EtOH).

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