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A practical synthesis of 3-ethyl-L-norvaline

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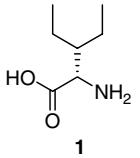
Abstract—An efficient process for the synthesis of 3-ethyl-L-norvaline has been developed. The route makes use of a Strecker reaction, whereby (*S*)-(−)-α-methylbenzylamine acts as a chiral auxiliary to provide nearly diastereomerically pure α-amino nitrile. Crystallization-induced asymmetric transformation enhances the yield and diastereomeric ratio and allows for efficient isolation of the product. The amino nitrile intermediate is converted to enantiomerically pure 3-ethyl-L-norvaline in three steps.

1. Introduction

The synthesis of unnatural, enantiomerically pure α-amino acids has become increasingly important.[1–3] Unnatural α-amino acids are used, for example, as intermediates in the synthesis of drug candidates and natural products, as substitutes of natural amino acids in peptides and proteins, and as ligands for chiral induction. Over the course of a drug development program, it became essential to design a practical method for the synthesis of 3-ethyl-L-norvaline **1**. Although several methods for the preparation of this compound have been described,[4–6] it was determined that these methods are too cumbersome and/or expensive for the purposes of a process scale preparation and, as such, we embarked on the development of a new route. This route involves a chiral Strecker reaction, where (*S*)-(−)-α-methylbenzylamine is used as a chiral auxiliary to provide an optically pure amino nitrile.[7–12] This intermediate can be readily converted to the corresponding amino acid by conventional functional group manipulation.



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2. Results and discussion

The first step in our synthesis of 3-ethyl-L-norvaline is the chiral Strecker reaction (Scheme 1). Thus, (*S*)-(−)-α-methylbenzylamine hydrochloride **3** was reacted with 2-ethylbutyraldehyde **2** and potassium cyanide to give amino nitriles **4** and **5** in a 4:1 ratio as determined by ^{1}H NMR spectroscopy (Table 1, entry 1). Subsequent recrystallization with MeOH/H_2O provided a 70% yield of amino nitrile **4** with a diastereomeric ratio of >40:1 (entry 2). The stereochemical assignment of **4** was based on literature precedence, where it has been shown that the use of (*S*)-(−)-α-methylbenzylamine as a chiral auxiliary in the Strecker reaction gives the (*S*)-configuration of the amino nitrile as the predominant stereoisomer.[7–12] Additional proof, as will be described herein, was based on the conversion of intermediate **4** to 3-ethyl-L-norvaline, whose specific rotation matched that of the value reported in the literature.[6]

As our goal was to find the most efficient and highest yielding process for scale-up, methods to improve the Strecker reaction were sought. We realized that the yield and efficiency of the reaction might be improved by in situ crystallization of the product. To test this proposition, the Strecker reaction was run with varying solvent systems (entries 3–6). The use of H_2O alone or with MeOH in ratios of 1:4 and 2:1 resulted in the product oiling out of solution. In the reaction with a 1:1 ratio of H_2O and MeOH, a white precipitate formed. After this mixture was stirred for 24 h, the precipitate was isolated by filtration and found to be amino nitrile **4**

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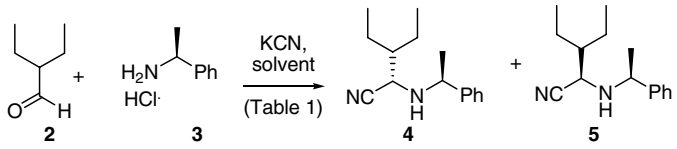


Scheme 1.

Table 1. Reaction conditions for the chiral Strecker reaction[a]

Entry	Solvent	Ratio	Conc. (M)	*T* (h)	Reaction appearance	Isolation procedure[b]	Yield (%)	Ratio of **4** to **5**[c]
1	MeOH		1.0	24	Solution	A	95	4:1
2	MeOH		1.0	24	Solution	B	70	>40:1
3	MeOH/H_2O	1:4	0.1	24	Oil	C	79	4:1
4	MeOH/H_2O	2:1	0.1	24	Oil	C	81	4:1
5	H_2O		0.1	24	Oil	C	79	4:1
6	MeOH/H_2O	1:1	0.1	24	Precipitate	D	74	>40:1
7	MeOH/H_2O	1:1	0.1	24	Precipitate	C	79	24:1
8	MeOH/H_2O	1:1[d]	0.4	24	Precipitate	D	98	19:1
9	MeOH/H_2O	1:1[d]	0.4	36	Precipitate	D	99	>40:1

[a] Reactions were carried out with equal molar amounts of 2-ethylbutyraldehyde, (*S*)-(−)-α-methylbenzylamine hydrochloride, and KCN at room temperature.
[b] A: filtration, concentration of filtrate; B: A, followed by recrystallization with MeOH/H_2O, 1:1; C: extraction with EtOAc from H_2O; D: filtration.
[c] Diastereomeric ratios were determined by ^1H NMR and HPLC. >40:1 means **5** was not detected by either method.
[d] (*S*)-(−)-α-Methylbenzylamine free base was used in place of the HCl salt and 1 equiv of HCl was added in 3 N aqueous solution.

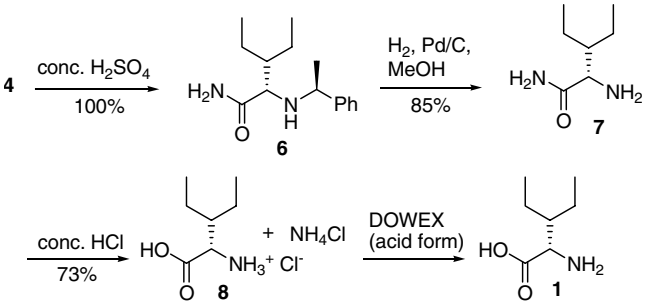
(diastereomeric ratio >40:1), which was isolated in 74% yield (entry 6).

Next, we were interested in determining if crystallization-induced asymmetric transformation occurred during the reaction. This is a process where a single diastereomer crystallizes preferentially from a solution of equilibrating stereoisomers, thus increasing the ratio of the less soluble diastereomer to more soluble diastereomer.[13] Indeed, in the reaction run as described in entry 6, but where the product was isolated by extraction from EtOAc instead of filtration, the diastereomeric ratio of amino nitrile **4** to amino nitrile **5** was 24:1 (entry 7). This is far greater than the 4:1 ratio that was obtained from the reaction, where the product remained in the solution (entry 1). Additionally, it has been demonstrated that the enhancement of diastereomeric selectivity is not due to the presence of H_2O alone, since the reactions described entries 3, 4, and 5 where H_2O is present, but precipitation did not occur, all gave diastereomeric ratios of 4:1.

The trial reactions described above were performed on an 8 mmol scale (entries 1–7). Upon scale-up to 1 mol, reactions were run at 0.35 M concentration of each reagent instead of 0.10 M. The higher concentration and increased scale provided a better yield, but lower diastereomeric purity (entry 8, 98% yield, 19:1 diastereomeric ratio). By increasing the run time from 24 to 36 h, a nearly quantitative yield product with a diastereomeric purity of >97% was obtained. The improvement in diastereomeric purity with increased time further validates the mechanism of crystallization-induced asymmetric transformation.

A precedence for in situ crystallization-induced asymmetric transformation of Strecker reactions exists; however, the phenomenon was never claimed with α-methylbenzylamine as the chiral auxiliary. Boesten et al. have recently reported the use of (*R*)-phenylglycine amide for in situ crystallization-induced asymmetric transformation of Strecker reactions.[14]

With large quantities of readily available amino nitrile **4**, the synthesis of amino acid **1** was completed in a three-step sequence (Scheme 2). Hydrolysis of nitrile **4** with sulfuric acid provided amide **6** in quantitative yield. Removal of the α-methylbenzyl chiral auxiliary by palladium-catalyzed hydrogenation under 100 psi of pressure provided amine **7**, which after hydrolysis with concentrated hydrochloric acid, yielded 3-ethyl-L-norvaline hydrochloride **8** with 1 equiv of ammonium chloride in 73% yield. The free base and salt free form of the amino acid was obtained by purification with DOWEX ion exchange resin (acidic form) to give amino acid **1** with a specific rotation that matches that in the literature.[6]



Scheme 2.

3. Conclusion

A scalable synthesis of 3-ethyl-L-norvaline has been described. The key step, a Strecker reaction, takes place

with crystallization-induced asymmetric transformation and provides an optimal yield of nearly diastereomerically pure α-amino nitrile **4**. From intermediate **4**, enantiomerically pure 3-ethyl-L-norvaline **1** was prepared in a high-yielding three-step sequence.

4. Experimental

4.1. General

The starting materials were purchased from commercial sources and used without further purification. Melting points were taken on a Mel-Temp 3.0 capillary melting point apparatus and are uncorrected. NMR spectra were determined on a 500 MHz Varian Inova or a 400 MHz Varian Unity Plus spectrometer using Me_4Si as the internal standard. Mass spectra were obtained on a Micromass LCT mass spectrometer. Optical rotation were obtained with a Jasco P-1020 polarimeter with a 30 mm cell. IR were obtained on a Avatar 360 FT-IR.

4.2. (2*S*)-3-Ethyl-2-{[(1*S*)-1-phenylethyl]amino}-pentanenitrile 4

4.2.1. Small scale preparation and trial reactions. A mixture of (*S*)-(−)-α-methylbenzylamine hydrochloride (315 mg, 2.00 mmol), potassium cyanide (130 mg, 2.00 mmol), and 2-ethylbutyraldehyde (250 μL, 2.00 mmol) in solvent (20 mL, see Table 1) was stirred for 24 h. Products were isolated by method A, B, C, or D. Product purity and diastereomeric ratios were determined by LC/MS and ^{1}H NMR as described below:

Method A: The reaction mixture was filtered to remove salts and then the filtrate was concentrated in vacuo.

Method B: The reaction mixture was filtered and then the filtrate was concentrated in vacuo. Recrystallization of the resulting residue from MeOH/H_2O, 1:1 provided the title compound.

Method C: Water was added to the reaction mixture. It was then extracted with ethyl acetate, dried over Na_2SO_4, and concentrated.

Method D: The reaction mixture was filtered and the precipitate collected and dried.

4.2.2. Large-scale preparation. A mixture of (*S*)-(−)-α-methylbenzylamine (135 g, 1.11 mol), potassium cyanide (72.5 g, 1.11 mol), and 2-ethylbutyraldehyde (118 g, 1.18 mol) in 3 M HCl (375 mL), water (1.2 L), and MeOH (1.6 L) was stirred at room temperature for 3 days. The resulting solids were collected via filtration and air dried to give 254 g (98% yield) of a white precipitate, with >30:1 diastereomeric purity as judged by HPLC [Phenomenex LUNA C8 (z) 100 × 2.0 mm, 3 mm particle size, A (95% water/5% acetonitrile) with ammonium acetate additive, B (95% acetonitrile/5% water) with ammonium acetate additive, gradient: 100% A for 1 min, to 100% B at time 40 min, (*S*,*S*)-isomer elutes at 33.65 min, (*R*,*S*)-isomer elutes at 33.10 min].

Mp = 57–58 °C; $[\alpha]_D^{25} = -187.4$ (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30–7.34 (m, 4H), 7.22–7.26 (m, 1H), 3.85–3.89 (d, 1H, *J* = 6.6 Hz), 3.00 (dd, 1H, *J* = 5.8, 11.6 Hz), 2.93 (d, 1H, *J* = 11.6 Hz), 1.49–1.58 (m, 1H), 1.35–1.48 (m, 3H), 1.29 (d, 3H, *J* = 6.6 Hz), 1.20–1.30 (m, 1H), 0.69–0.83 (m, 6H); MS (ES+) *m*/*z* 272 (M+ACN+H), 231 (M+H), 204; IR (ATR) 3300, 2950, 2925, 2875, 1450 cm^{-1}; Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 77.90; H, 9.75; N, 12.32.

4.3. 3-Ethyl-N^2-[(1*S*)-1-phenylethyl]-L-norvalinamide 6

Concentrated sulfuric acid (400 mL) was cooled to 4 °C and amino nitrile **4** (200 g, 868 mmol) added. After the mixture was stirred at room temperature for 24 h it was poured onto ice and then concentrated NH_4OH (1 L) added until the pH was 8. The mixture was extracted with EtOAc, dried over Na_2SO_4, and concentrated to give 215 g (100% yield) of a pale yellow oil. $[\alpha]_D^{25} = -68.4$ (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.26–7.30 (m, 5H), 7.17–7.21 (m, 1H), 6.97 (s, 1H), 3.50 (q, 1H, *J* = 6.5 Hz), 2.57 (br s, 1H), 2.04 (br s, 1H), 1.40–1.47 (m, 1H), 1.21 (d, 3H, *J* = 6.6 Hz), 1.14–1.25 (m, 4H), 0.68 (t, 3H, *J* = 7.2 Hz), 0.57 (t, 3H, *J* = 7.3 Hz); MS (ES+) *m*/*z* 249 (M+H); IR (ATR) 3450, 3300, 3200, 1670 cm^{-1}; Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.24; H, 10.04; N, 11.01.

4.4. 3-Ethyl-L-norvalinamide 7

Benzyl amino amide **6** (40 g, 0.16 mol) and 5% Pd/C (5.9 g) in MeOH (400 mL) were hydrogenated at 100 psi for 24 h. The catalyst was removed via filtration through Celite. Concentration of the filtrate gave 19.7 g (85% yield) of a solid. $[\alpha]_D^{25} = +3.4$ (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 (s, 1H), 6.89 (s, 1H), 3.07 (d, 1H, *J* = 4.6 Hz), 1.52 (br s, 2H), 1.40–1.46 (m, 1H), 1.24–1.34 (m, 3H), 1.09–1.20 (m, 1H), 0.84 (t, 3H, *J* = 7.3 Hz), 0.79 (t, 3H, *J* = 7.5 Hz); MS (ES+) *m*/*z* 186 (M+ACN+H), 145 (M+H); IR (ATR) 3500, 3200, 2970, 2925, 2880, 1650 cm^{-1}; Anal. Calcd for $C_7H_{16}N_2O$+0.1 H_2O: C, 57.58; H, 11.18; N, 19.18. Found: C, 57.83; H, 11.19; N, 18.92.

4.5. 3-Ethyl-L-norvaline, hydrochloride 8

Amino amide **7** (47.9 g, 0.33 mol) in concd HCl was heated at reflux for 24 h. The mixture was then concentrated under vacuum to give a solid. Trituration with acetone gave 56.4 g (73% yield) of a solid, which consisted of amino acid hydrochloride salt and 1 equiv of NH_4Cl. $[\alpha]_D^{25} = +13.9$ (*c* 1.0, H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (br s, 3H), 7.19 (t, 4H, *J* = 50.7 Hz), 3.84 (d, 1H, *J* = 3.05 Hz), 1.65–1.69 (m, 1H), 1.40–1.48 (m, 1H), 1.30–1.47 (m, 2H), 1.20–1.29 (m, 1H), 0.86–0.91 (m, 6H); MS (ES+) *m*/*z* 146 (M+H); IR (ATR) 3350, 2900, 1720 cm^{-1}.

4.6. 3-Ethyl-L-norvaline 1

3-Ethyl-L-norvaline, hydrochloride **8** (250 mg, 1.07 mmol) was dissolved in 1 M HCl (10 mL) and applied to a column of Dowex-50W-hydrogen, strongly acidic (50W X 8-400) ion-exchange resin. Salts were eluted with $MeOH/H_2O$, 1:1 (50 mL), and then the amino acid was eluted with 1 M ammonium hydroxide (150 mL) to give 123 mg (79% recovery) of the title compound. $[\alpha]_D^{25} = +40$ (*c* 0.5, 5 M HCl); ^1H NMR (400 MHz, DMSO-d_6) δ 7.10 (br s, 3H), 3.15 (d, $J = 2.6$ Hz), 1.60 (m, 1H), 1.08–1.42 (m, 4H), 0.70–0.90 (m, 6H); MS (ES-) *m*/*z* 144 (M−H); Anal. Calcd for $C_7H_{15}NO_2$+0.1 H_2O: C, 57.19; H, 10.42; N, 9.53. Found: C, 56.91; H, 10.28; N, 9.68.

References

1. Cativiela, C.; Diaz-De-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517.
2. Calmes, M.; Daunis, J. *Amino Acids* **1999**, *16*, 215.
3. Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989.
4. Hassan, N. A.; Bayer, E.; Jochims, J. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, *22*, 3747.
5. Praetorius, H. J.; Flossdorf, J.; Kula, M. R. *Chem. Ber.* **1975**, *108*, 3079.
6. Eisler, K.; Rudinger, J.; Sorm, F. *Collection Czechoslov. Chem. Commun.* **1966**, *31*, 4563.
7. Speelman, J. C.; Talma, A. G.; Kellogg, R. M.; Meetsma, A.; de Boer, J. L.; Beurskens, P. T.; Bosman, W. P. *J. Org. Chem.* **1989**, *54*, 1055.
8. Wede, J.; Volk, F.-J.; Frahm, A. W. *Tetrahedron: Asymmetry* **2000**, *11*, 3252.
9. Stout, D. M.; Black, L. A.; Matier, W. L. *J. Org. Chem.* **1983**, *48*, 5369; Schlosser, M.; Brügger, N.; Schmidt, W.; Amrhein, N. *Tetrahedron* **2004**, *60*, 7731.
10. Truong, M.; Lecornué, F.; Fadel, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1063.
11. Do, K. Q.; Thanei, P.; Caviezel, M.; Schwyzer, R. *Helv. Chim. Acta* **1979**, *62*, 956.
12. Patel, M. S.; Worsley, M. *Canadian J. Chem.* **1970**, *48*, 1881.
13. Jacques, J.; Collet, A.; Wilen, S. H. In *Enantiomers, Racemates, and Resolutions*. In *Crystallization-Induced Asymmetric Transformations*; John Wiley & Sons: New York, NY, 1981; Chapter 6, pp 369–377.
14. Boesten, W. H. J.; Seerden, J.-P. G.; de Lange, B.; Dielemans, H. J. A.; Elsenberg, H. L. M.; Kaptein, B.; Moody, H. M.; Kellogg, R. M.; Broxterman, Q. B. *Org. Lett.* **2001**, *3*, 1121.