One-pot Sequence for the Decarboxylation of α-Amino Acids

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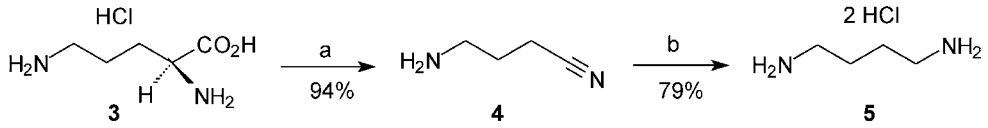
Abstract: Treatment of an α-amino acid with *N*-bromosuccinimide in water at pH 5 or in an alcoholic-aqueous ammonium chloride mixture, followed by addition of nickel(II) chloride and sodium borohydride, effected an overall decarboxylation via an intermediate nitrile to afford the corresponding amine in good yield.

Key words: α-amino acid, nitrile, amine, decarboxylation

Decarboxylation of α-amino acids is a long-known reaction,[1] which leads to amines with a range of applications from the synthesis of biologically active compounds[2] to the preparation of chiral auxiliaries for asymmetric synthesis.[3] The most commonly used method employs thermolysis of the amino acid in the presence of catalytic amount of an aldehyde (e.g. pyridine-4-carboxaldehyde) or ketone[4] (e.g. 2-cyclohexen-1-one[5]). These methods are modelled on enzymatic methods for the decarboxylation of α-amino acids, which utilise a decarboxylase with a pyridoxal or pyruvoyl cofactor.[6] Other non-enzymatic methods include irradiation with UV light,[7] heating in diphenylmethane solvent[8] or thermolysis in a high boiling solvent in the presence of a peroxide catalyst.[9] However, some unnatural α-amino acids do not undergo decarboxylation under the conditions described and a general non-thermal procedure is needed. We report herein a new procedure for the decarboxylation of α-amino acids that is rather general in scope and gives good yields of amino compounds.

During studies of the synthesis of polyamines[10] using cobalt(III) templates, it was necessary to convert precursor 'carboxypolyamines' **2a**–**c** into the corresponding polyamines **1a**–**c**. Several attempts at decarboxylation of α-amino acids **2a**–**c** in acetophenone, ethylene glycol/*p*-anisaldehyde (as well as other aromatic aldehydes), cyclohexanol/2-cyclohexen-1-one at elevated temperatures were unsuccessful and the starting material was recovered. This led us to explore the possibility of a 'one-pot' combination of two known reactions: oxidative decarboxylation[11] of α-amino acids to nitriles induced by *N*-bromosuccinimide,[12] reduction of nitriles to amines effected by sodium borohydride–nickel chloride.[13] In this way, we have developed an efficient method for the decarboxylation of a variety of α-amino acids, including **2a**–**c**. Initially, it was found that oxidative decarboxylation of the model compound L-ornithine monohydrochloride **3** with *N*-bromosuccinimide in a phosphate buffer at pH 5 afforded the corresponding nitrile **4** (94%). Subsequent reduction of nitrile **4** in ethanol with the system nickel chloride hexahydrate/sodium borohydride afforded putrescine **5** (79%, overall yield 74%) (Scheme 1).

It was then found that when compound **3** was taken up in a phosphate buffer solution (pH 5) and a dimethyl formamide solution of *N*-bromosuccinimide was added dropwise at room temperature, decarboxylation started immediately. When the evolution of CO_2 stopped, nickel(II) chloride hexahydrate was added, followed by addition by portions of sodium borohydride. Filtration of the reaction mixture followed by loading onto an ion exchange column afforded, after elution with a gradient of aqueous hydrochloric acid, putrescine dihydrochloride **5** (71% overall)[14a] (Scheme 2). Application of this latter procedure to the decarboxylation of 'carboxypolyamines' **2a**–**c** furnished the corresponding polyamines **1a**–**c** in good yields (Table 1, entries 1–3).



Scheme 1 Two-step decarboxylation of α-amino acid **3**. *Reagents and conditions:* a) Phosphate buffer (pH 5), NBS in CH_3CN, r.t.; b) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, EtOH, r.t.

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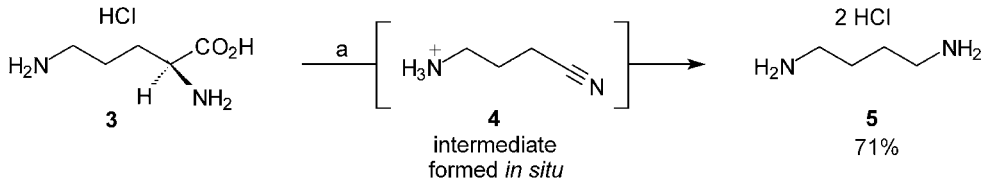


Scheme 2 'One-pot' decarboxylation of α-amino acid **3**. *Reagents and conditions:* a) Phosphate buffer (pH 5), NBS in DMF then $NiCl_2 \cdot 6H_2O$, $NaBH_4$, r.t.

Table 1 'One-pot' Decarboxylation of a Series of Natural and non-Natural α-Amino Acids Using the Conditions Given in Ref.[14a]

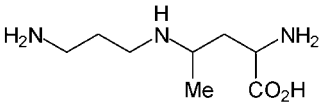
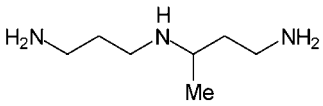
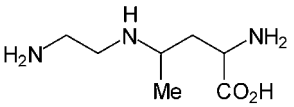
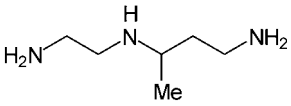
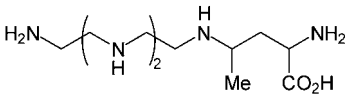
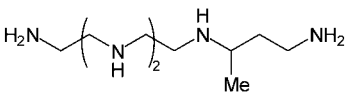
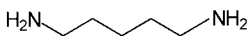
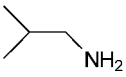
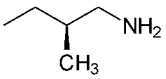
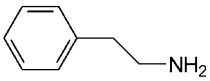
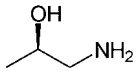
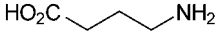
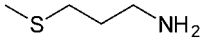
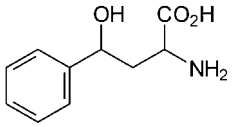
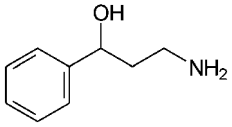
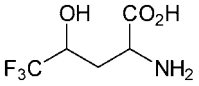
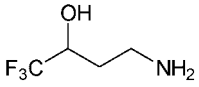
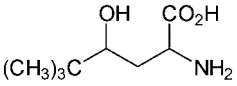
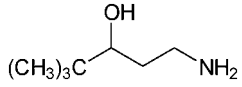
Entry	Amino acid	Product[a]	Yield
1	 **2a**	 **1a**	73%
2	 **2b**	 **1b**	62%
3	 **2c**	 **1c**	69%
4	L-lysine	 **6**	77%
5	L-valine	 **7**	68%
6	L-*iso*leucine	 **8**	81%
7	L-phenylalanine	 **9a**	76%
8	L-(2*R*)-threonine	 **10**	59%
9	L-glutamic acid	 **11**	68%
10	L-asparagine	 **12**	70%
11	L-methionine	 **13**	Impure[b]

Table 1 'One-pot' Decarboxylation of a Series of Natural and non-Natural α-Amino Acids Using the Conditions Given in Ref.[14a] (continued)

Entry	Amino acid	Product[a]	Yield
12	 **14**	 **15**	73%
13	 **16**	 **17**	61%
14	 **18**	 **19**	67%

[a] Products were isolated as their hydrochloride salts.
[b] See text.

A series of natural and non-natural α-amino acids were reacted under the conditions described (Table 1). As expected, when L-lysine monohydrochloride was employed as substrate, 1,5-diaminopentane dihydrochloride (**6**) was obtained (77%). Decarboxylation of L-valine, L-(2*S*)-*iso*-leucine and L-phenylalanine afforded *iso*butylamine (**7**), (2*S*)-methyl-1-aminobutane (**8**), and 2-phenylethylamine (**9a**) as their monohydrochloride salts in 68%, 81% and 76% yields, respectively (Table 1, entries 5–7).

To explore the effect of a functional group in the side chain of the amino acid, we attempted reactions on L-(2*R*)-threonine, L-glutamic acid, L-asparagine and L-methionine, respectively. Decarboxylation proceeded well with L-threonine, L-glutamic acid and L-asparagine affording (2*R*)-hydroxypropylamine (**10**), 4-aminobutyric acid (**11**) and 3-aminopropionamide (**12**) as their mono hydrochloride salts in moderate to good yields (Table 1, entries 8–10). For L-methionine, which is the only amino acid investigated that did not undergo decarboxylation in satisfactory yield, an unidentified by-product was obtained in addition to 3-methylthiopropyl-1-amine (**13**) (Table 1, entry 11).

Application of the method described to non-proteinogenic α-amino acids proved efficient for the preparation of the corresponding amino alcohol. Thus, the non-natural racemic γ-hydroxy-α-amino acids **14**, **16**, **18**,[10] were successfully decarboxylated yielding the corresponding γ-amino alcohols as their monohydrochloride salts **15**,[15] **17**, **19**, respectively, in good yields (Table 1, entries 12–14).

Kinetic studies of the oxidative decarboxylation of α-amino acids with *N*-bromosuccinimide[12] have shown that a pH value of 5 was critical for directing the reaction towards the corresponding nitrile rather than the aldehyde. Although phosphate buffer proved to be an efficient reaction medium for achieving our conversions, the use of aqueous ammonium chloride was more practical and yielded the desired compounds in slightly better yields on selected amino acids (Table 2, entries 1 and 2). When the reaction with L-phenylalanine was performed in slightly wet methanol saturated with ammonium chloride, the decarboxylation did not reach completion and amine **9a** was obtained only in low yield (Table 2, entry 3). Presumably, the low conversion of this reaction is due to an insufficient amount of the oxidizing species H_2O^+Br in the reaction mixture. However, when the volume of saturated aqueous ammonium chloride was raised to 5%, the reaction proceeded very well in methanol, ethanol and dimethyl formamide (Table 2, entries 4–6).

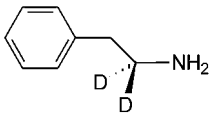
The best results were obtained in ethanol–5% saturated aqueous ammonium chloride and this solvent was chosen to conduct decarboxylation of L-(2*S*)-isoleucine and L-(2*R*)-threonine (Table 2, entries 7 and 8, for a typical procedure see ref.[14b]). The advantage of an alcoholic solvent was the ease of extraction of the product from the reaction mixture. However, for amino acids poorly soluble in organic solvents, the procedure of ref.[14a] (cf. Table 1) is preferred. The method described has been extended to the preparation of a specifically labeled amine. Thus, treatment of L-phenylalanine with NBS in EtOD–5% D_2O saturated with ND_4Cl, followed by reduction with $NaBD_4$–$NiCl_2$, gave [1-$^2H_2$]2-phenylethylamine **9b** in good yield (Table 2, entry 9).

In conclusion, we have reported two efficient one-pot procedures for the decarboxylation of α-amino acids to the corresponding amines. The procedures involve a sequence of oxidative decarboxylation and reduction and works well on a variety of natural and non-natural α-amino acids. The reactions can be performed either in buffered aqueous solution at pH 5 or in an organic solvent containing 5% saturated aqueous ammonium chloride.

Acknowledgement

We thank the EPSRC for support.

Table 2 Variation of the Experimental Conditions for the Decarboxylation of α-Amino Acids

Entry	Substrate	Conditions	Product[a]	Yield (Conversion[b])
1	L-Phenylalanine	H_2O, NH_4Cl, NBS in DMF then $NiCl_2{\cdot}6H_2O$, $NaBH_4$	**9a**	82% (100%)
2	L-(2*S*)-*iso*Leucine	H_2O, NH_4Cl, NBS in DMF then $NiCl_2{\cdot}6H_2O$, $NaBH_4$	**9a**	85% (100%)
3	L-Phenylalanine	wet MeOH, NH_4Cl NBS in DMF then $NiCl_2{\cdot}6H_2O$, $NaBH_4$	**9a**[c]	30% (41%)
4	L-Phenylalanine	MeOH–H_2O (95:5), NH_4Cl, NBS in DMF then $NiCl_2{\cdot}6H_2O$, $NaBH_4$	**9a**[c]	65% (79%)
5	L-Phenylalanine	EtOH–H_2O (95:5), NH_4Cl, NBS in DMF then $NiCl_2{\cdot}6H_2O$, $NaBH_4$	**9a**[c]	71% (89%)
6	L-Phenylalanine	DMF–H_2O (95:5), NH_4Cl, NBS in DMF then $NiCl_2{\cdot}6H_2O$, $NaBH_4$	**9a**	65% (68%)
7	L-(2*S*)-*iso*Leucine	EtOH–H_2O (95:5), NH_4Cl, NBS in DMF then $NiCl_2{\cdot}6H_2O$, $NaBH_4$	**8**[c]	73% (87%)
8	L-(2*R*)-Threonine	EtOH–H_2O (95:5), NH_4Cl, NBS in DMF then $NiCl_2{\cdot}6H_2O$, $NaBH_4$	**10**	55% (82%)
9	L-Phenylalanine	EtOD–D_2O (95:5), ND_4Cl, NBS in DMF then $NiCl_2$, $NaBD_4$	 **9b**	68% (75%)

[a] Isolated as the hydrochloride salt.
[b] Based on the amount of starting material recovered.
[c] The product was isolated as the free amine after reduction of the volume of the reaction mixture and extraction with diethyl ether from a basic aqueous solution.

References

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(2) See for example: (a) Pasini, A.; Zunio, F. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 615. (b) Miyadera, T.; Sugimura, Y.; Hashimoto, T.; Tanaka, T.; Iino, K.; Shibata, T.; Sugawara, S. *J. Antibiotics* **1983**, *36*, 1034.
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(10) Laval, G.; Clegg, W.; Crane, C. G.; Hammershøi, A.; Sargeson, A. M.; Golding, B. T. *Chem. Commun.* **2002**, 1874.
(11) (a) Gowda, B. T.; Mahadevappa, D. S. *J. Chem. Soc., Perkin Trans. 2* **1983**, 323. (b) For the oxidative decarboxylation of N-protected amino acids see for example: Boto, A.; Hernandez, R.; De Leon, Y.; Suarez, E. *J. Org. Chem.* **2001**, *66*, 7796.
(12) Gopalakrishnan, G.; Hogg, J. L. *J. Org. Chem.* **1985**, *50*, 1206.
(13) Satoh, T.; Suzuki, S. *Tetrahedron Lett.* **1969**, 4555.
(14) **Typical Procedures.** (a) L-Asparagine (2.90 g, 19.3 mmol) was taken up in a pH 5 phosphate buffer (prepared from 100 mL of a 0.1 M solution of citric acid and 100 mL of a 0.2 M solution of disodium hydrogen orthophosphate dodecahydrate) (90 mL). To the stirred amino acid solution was added NBS (10.3 g, 57.9 mmol) in DMF (20 mL) at r.t., where upon CO_2 gas was evolved immediately. After 30 min, nickel(II) dichloride hexahydrate (22.9 g, 96.5 mmol) was dissolved into the reaction mixture and $NaBH_4$ (5.84 g, 154 mmol) was added in portions with vigorous stirring. Addition of the latter was exothermic and hydrogen gas was vigorously evolved. After 20 min at r.t., the reaction mixture was filtered through Celite® and diluted with distilled H_2O (500 mL). The light green filtrate was loaded on a column (25 cm × 2 cm) of Dowex 50WX8-200 ion exchange resin, the column was washed well with H_2O (400 mL) and the

amine was eluted with a concentration gradient of ammonium hydroxide. Removal of the solvent under reduced pressure afforded the amine, which was treated with 1.0 M HCl to give 3-aminopropionamide (**12**) as its hydrochloride (1.68 g, 13.5 mmol). (b) L-Phenylalanine (400 mg, 2.42 mmol) was taken up in a mixture of EtOH (40 mL), H_2O (2 mL) and a sat. aq solution of NH_4Cl (1.5 mL). To the stirred amino acid solution was added NBS (1.07 g, 6.05 mmol) in DMF (5 mL) at r.t., whereupon CO_2 was evolved immediately. After 20 min, nickel(II) dichloride hexahydrate (2.30 g, 9.68 mmol) was dissolved into the reaction mixture and $NaBH_4$ (915 mg, 24.2 mmol) was added in portions with vigorous stirring. Addition of the latter was exothermic and hydrogen was vigorously evolved. After 30 min at r.t., the reaction was filtered through Celite®, and the ethanol was removed. The liquid residue was taken up in water (20 mL) and basified to pH 10 with aq 1.0 M NaOH. The aq solution was extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with a sat. aq solution of $NaHCO_3$ (20 mL) and dried over $MgSO_4$. Removal of the solvent afforded 2-phenylethylamine (**9a**) (208 mg, 71%) as a colourless oil.

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