Organic Process Research & Development **2003**, *7*, 164–167

Reductions of Aromatic Amino Acids and Derivatives

David J. Ager*,† and Indra Prakash*,‡

The NutraSweet Company, 601 East Kensington Road, Mount Prospect, Illinois 60056, U.S.A.

Abstract:

Catalytic reduction of phenylalanine and phenylglycine derivatives can be achieved with rhodium on carbon or alumina to give good yields of the corresponding cyclohexyl derivatives. The procedure can be scaled.

The reduction of aromatic amino acids leads to unnatural amino acids that have been incorporated into a number of pharmaceutical candidates. For example, L-cyclohexylalanine (**1**), L-cyclohexylalaninol (**2**), and their derivatives are used for the construction of peptide isosteres related to the renin−angiotensin system. These have been utilized by several research groups involved in the design and synthesis of peptidomimetic therapeutic agents.[1] L-Cyclohexylalanine amide (**3**) has been used in the synthesis of tetrapeptide analogues of pentagastrin and cholecystokinin drugs.[2]

Previous reported methods for the synthesis of L-cyclohexylalanine (**1**) involve the reduction of L-phenylalanine (**4**) using platinum oxide or platinum on carbon in acetic acid.[3] Rhodium in the presence of acid has been used for the reduction of phenylglycine (vide infra).[4] Synthesis of L-cyclohexylalanine amide (**3**) is reported in a patent without any experimental detail.[2] L-Cyclohexylalaninol (**2**)[5] was prepared by the sodium or calcium borohydride reduction of the L-Boc-cyclohexylalanine methyl ester (**6**),[6] followed by hydrolysis of the Boc group (Scheme 1). A method for the hydrogenation of aromatic amines to their corresponding alkyl derivatives with $Rh-Al_2O_3$ has been reported for this amino alcohol but with moderate yield.[7] We now report a simple method for the reduction of aromatic amino acid derivatives to corresponding cyclohexyl compounds with hydrogen at low pressure and rhodium as the catalyst under conditions used in "conventional" equipment and without racemization of the amino acids.

Catalytic reduction of L-phenylalanine (**4**) over rhodium on carbon under acidic conditions (hydrochloric, sulfuric, or phosphoric acids) gave **1** in good yields. The reduction could not be achieved under neutral conditions. Interestingly, when the Rh−C was replaced with $Rh-Al_2O_3$ catalyst, no acid was required to achieve the reduction, and high yields of the saturated compound were obtained. Alternatively, **1** could also prepared by the reduction of L-Boc-phenylalanine methyl ester (**7**) followed by acidic treatment to remove the protecting group and hydrolysis of the ester (**8**) (Scheme 1) in a manner similar to that previously reported.[6] The less direct route was used to illustrate that derivatives of the parent amino acid **1** are also available by reduction of the appropriate substrate rather than by performing reactions or protection/deprotection chemistry on **1**.

For either reaction pathway, no racemization of the amino acid was observed. The product **1** was isolated by standard precipitation techniques near the isoelectric point. For the more polar amino acids, water was used as the solvent, while methanol had to be employed for the *N*-protected ester **7**. In a similar manner, the reduction was then extended to the synthesis of L-cyclohexylalanine amide (**3**) from L-phenylalanine amide (**9**) (Scheme 2).

The procedure can also be applied to L-phenylglycine (**10**) in addition to the D-isomer. Again, no racemization was observed in the product **11**. As well as acidic conditions, the sodium salt of the amino acid can be used to enhance solubility in water (Scheme 3). This methodology is also available for other arylamino acids. In our hands, the basic method performed better than those with acidic conditions,[4] and this approach is more amenable to scale-up as reactor compatibility problems with the acidic conditions are avoided.

In addition to α-amino acids, the amino alcohol **2** was prepared by the reduction of L-phenylalaninol (**12**) over Rh−C under acidic conditions (Scheme 4). Again, the reaction did not proceed under neutral conditions with either Rh−C or $Rh-Al_2O_3$ although a wide range of catalysts of these types was screened. The yield obtained was higher (97%) than that previously reported (47%).[7]

Alternatively, **2** was also prepared from L-Boc-phenylalaninol (**13**) by catalytic reduction followed by acidic

* Authors for correspondence. Telephone: (919) 844-2985. Fax: (919) 870-7902. E-mail: scribusted@aol.com and indra.prakash@nutrasweet.com.

† Current address: RCCorp, 805 Darfield Drive, Raleigh, NC 27615.

‡ Current address: NutraSweet, 699 Wheeling Road, Mount Prospect, IL 60056.

(1) Kleinert, H. D. *Am. J. Hypertens.* **1967**, *2*, 800; Luly, J. R.; BaMaung, N.; Soderquist, J.; Fung, A. K. L.; Stein, H.; Kleinert, H. D.; Marcotte, P. A.; Egan, D. A.; Bopp, B.; Merits, I.; Bolis, G.; Greer, J.; Perun, T. J.; Plattner, J. J. *J. Med. Chem.* **1988**, *31*, 2264; Luly, J. R. *J. Org. Chem.* **1988**, *53*, 6109; Rivero, R. A.; Greenlee, W. J. *Tetrahedron Lett.* **1992**, *32*, 2453.

(2) Kalindjian, S. B.; Broughton, H. B.; Low, C. M. R.; McDonald, I. M.; Hull, R. A. D.; Shankley, N. P.; Buck, I. M.; Steel, K. I. M.; Davies, J. M. R. PCT Int. Appl. WO 9211284, 1992; *Chem. Abstr.* **1992**, *118*, 39421.

(3) Hoekstra, W. J.; Sunder, S. S.; Gregge, R. J.; Ashton, L. A.; Stewart, K. T.; King, C. H. R. *Tetrahedron* **1992**, *48*, 307; Schuda, P. F.; Greenlee, W. J.; Chakravarty, P. K.; Eskola, P. *J. Org. Chem.* **1988**, *53*, 873; Wieland, T.; Rohr, G.; Faulstich, H.; Zobeley, S.; Trischmann, H. *Liebigs Ann. Chem.* **1977**, 381.

(4) Minnaard, A. J.; Boesten, W. H. J.; Zeegers, H. J. M. *Synth. Commun.* **1999**, *29*, 4327.

(5) Krysan, D. J.; Haight, A. R.; Lallaman, J. E.; Langridge, D. C.; Menzia, J. A.; Narayanan, B. A.; Pariza, R. J.; Reno, D. S.; Rockway, T. W. et al *Org. Prep. Proced. Int.* **1993**, *25*, 437.

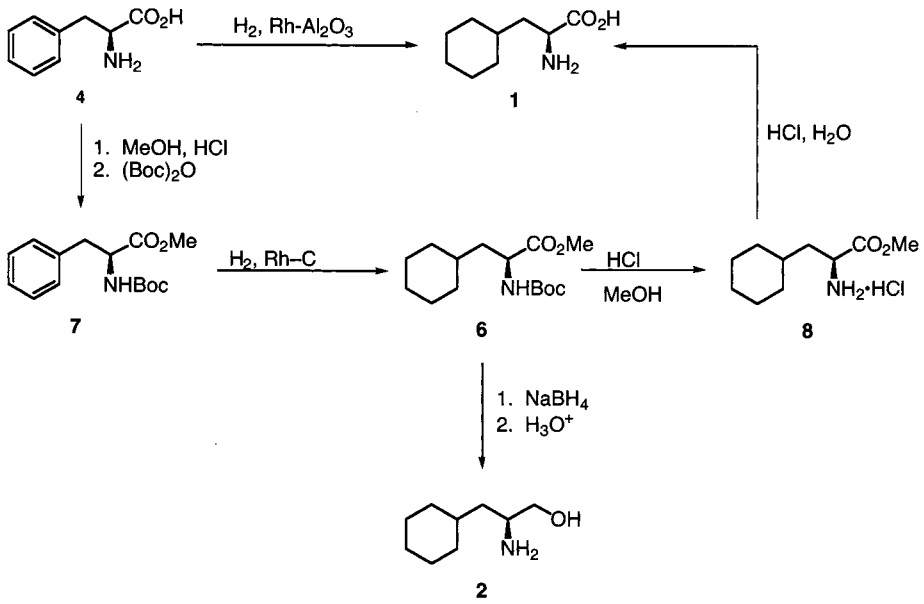
(6) Reduction of **7** to **6** by the use of $Rh-Al_2O_3$ at 30−55 psi has been reported in the literature, but this reduction did not work well in our hands. Albright, J. D.; Howell, C. F.; Sum, F. W. *Heterocycles* **1993**, *35*, 737; Kurauchi, M. and Nakamura, T. Eur. Pat. Appl. EP 493087 1992; Branca, Q. Edenhofer, A.; Gutknecht, E.-M.; Neidhart, W.; Ramoz, H. Eur. Pat. Appl. EP310918; Boger, J.; Payne, L. S.; Perlow, D. S.; Lohr, N. S.; Poe, M.; Blaine, E. H.; Ulm, E. H.; Schorn, T. W.; LaMont, B. I.; Lin, T.-Y.; Kawai, M.; Rich, D. H.; Veber, D. F. *J. Med. Chem.* **1985**, *28*, 1779.

(7) Strotmann, M.; Butenschön, H. *Synth. Commun.* 2000, *30*, 4173.

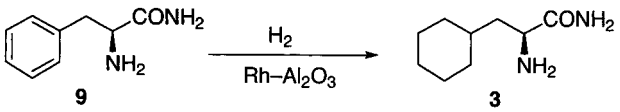
10.1021/op0200773 CCC: $25.00

Published on Web 02/12/2003

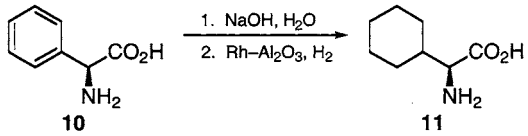
Scheme 1



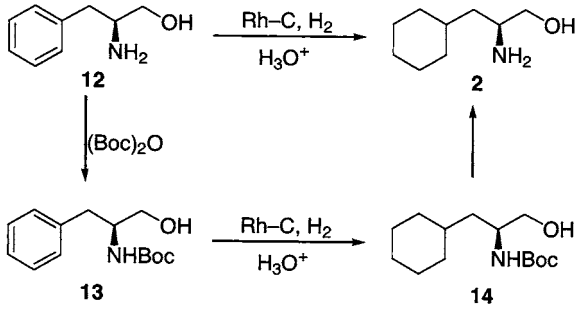
Scheme 2



Scheme 3



Scheme 4



hydrolysis of the *N*-Boc compound **14** (Scheme 4). This last sequence was also used to prepare D-cyclohexylalaninol.

The experimental procedures are based on laboratory-scale reactions. In most cases, the reaction time was dependent upon the exact nature of the catalyst employed, and reaction times should be considered as maxima. In some cases, reduction at larger scale was complete within a few hours. Presumably, at larger scale the hydrogen transfer is more efficient, and this results in the shorter reaction times.

The catalysts tried are listed in the Experimental Section. In many cases great variation was seen between different suppliers of the same catalyst type. As noted, we had difficulty repeating a literature reaction.[6] In one example we saw variation between lots by the same supplier under identical reaction conditions. Obviously, these reductions are susceptible to the reaction conditions and catalyst used. As a consequence, others are encouraged to perform optimization experiments with their catalyst and substrate. In this work, reductions were successfully performed with catalysts from at least two suppliers at laboratory scale.

Although it seems a straightforward transformation, reductions of arylamino acids to the corresponding alkyl derivatives are not simple procedures as the amino acids can racemize under the reaction conditions. Use of rhodium under either acidic or basic conditions allows for the reduction of the aromatic ring with hydrogen at pressures that can be accommodated by normal hydrogenation equipment at scale. No racemization was observed and the procedure was used to prepare multikilogram quantities of the products described.

Experimental Section

The melting points are uncorrected. IR spectra (Nujol) were recorded on a Nicolet FT-IR spectrometer. ^{1}H NMR spectra were recorded on a GE 300 spectrometer in $CDCl_3$ using TMS as internal standard. Optical rotation was measured on a Perkin-Elmer 241 Polarimeter. The optical purity was also checked by chiral HPLC. To follow reactions, TLC was usually employed. Unless the solvent system is specified, the general solvent system used for elution was chloroform:methanol:acetic acid:6.5:3.5:0.005. The disappearance of the starting materials was monitored by loss of UV absorbance. Alkyl amino acid derivatives were visualized by use of ninhydrin.

The catalysts studied were obtained from Johnson Matthey, Degussa, and Engelhard. Rhodium on carbon and alumina was used from each of these suppliers and screened. Loadings were 5 and 10%. For the experiments below, 5% loadings with Johnson Matthey catalysts were found to be best.

Laboratory hydrogenations were performed in mechanically stirred Parr reactors with external heating. In some cases, Fischer−Porter bottles fitted with appropriate inlet and outlet tubes and valves were used for screenings; external

heat was applied through an oil bath, and stirring was magnetic. For the kilogram preparations, a 30-gal Pfaudler reactor that was fitted with a sparge ring and hydrogen pump capabilitied was used. The system included pressure sensors that were computer-monitored to allow for the reactions to be followed by hydrogen uptake.

L-Cyclohexylalanine (1): Direct Hydrogenations. *Without Acid.* To a slurry of L-phenylalanine (**4**) (5 g, 0.03 mol) in water (50 mL) was added wet 5% Rh on alumina (0.5 g, 20% wet with water) and the mixture hydrogenated under hydrogen at 100 °C/250 psig for 24 h. The TLC (MeOH:H_2O = 8:2) of the reaction mixture showed the absence of **4.** The resultant slurry was dissolved in 1 N sodium hydroxide (30 mL), and the mixture was filtered through a 1-cm bed of Dicalite. The Dicalite bed was washed with water (30 mL). The filtrate and washings were combined, and the pH was adjusted to ~5.5 with 1 M hydrochloric acid. The precipitated solid was filtered, washed with water (30 mL), and dried in a vacuum oven at 50 °C/24 h to give 4.5 g (88%) of **1** as a white solid, mp 298−300 °C (lit.[3] 297−300 °C), [α] +14.06° (*c* = 2, TFA).

This sequence was performed with L-phenylalanine (**4**) (5.0 kg) in water (50 kg). The catalyst was Johnson Matthey 5% Rh on alumina (lot no. 021215001). The reaction was monitored by hydrogen uptake and was complete in about 8 h. Work-up was as described above.

With Acid. To a solution of **4** (9.9 g, 0.06 mol) in aqueous phosphoric acid (150 mL, 20%) was added rhodium on carbon (1 g, 5%, 65% wet with water) and the mixture hydrogenated at 60 °C/50 psig for 24 h. The mixture was cooled to room temperature and filtered through a 1-cm Dicalite bed. The bed was washed with water (30 mL). The filtrate and washings were combined, and the pH was adjusted to ~5.5 with 2 M sodium hydoxide. The precipitated solid was filtered, washed with water (2 × 100 mL), and dried in a vacuum oven at 50 °C to yield 10 g (97%) of **1** as a white solid.

This reaction was also carried out in 3 M hydrochloric and 1.5 M sulfuric acids. Yields were 90−95%.

Indirect Method: L-Boc-cyclohexylalanine Methyl Ester (6). To a solution of L-Boc-phenylalanine methyl ester (**7**) (10 g, 0.036 mol) in methanol (10 mL) was added wet 5% rhodium on carbon (0.5 g in 3 mL of water), and the mixture was hydrogenated at 60 °C/40−45 psig for 16 h. The TLC (EtOAc:hexane, 1:9) of the reaction mixture showed the absence of **7**. The mixture was cooled to room temperature and filtered through a 1-cm bed of Dicalite. The Dicalite bed was washed with methanol (2 × 15 mL). The filtrate and washings were concentrated to an oil. This oil was dissolved in 30 mL of ethyl acetate and dried ($MgSO_4$). The solution was filtered and concentrated in vacuo to give **6** as a white solid (9.5 g, 93%), mp 44−46 °C (lit.[6] 48−49 °C), [α] −19.59° (*c* = 10, MeOH).

L-Cyclohexylalanine Methyl Ester (8). To a solution of **6** (10 g, 0.035 mol) in methanol (50 mL) was added concentrated hydrochloric acid (25 mL). The mixture was stirred at room temperature for 4 h and then concentrated in vacuo to remove some of the solvent. The precipated solid was filtered and dried in a vacuum oven at 40 °C/24 h to yield a white solid 6.8 g (88%) of **8** as its hydrochloride salt.

L-Cyclohexylalanine (1). A slurry of **8** as its hydrochloride salt (10 g, 0.045) in concentrated hydrochloric acid was heated under reflux for 24 h. A clear solution was obtained. The mixture was cooled to room temperature. The precipitated white solid was filtered and dried in a vacuum oven at 40 °C/24 h to yield 8 g (81%) of **1** as its hydrochloride salt: mp 232−237 °C dec, [α] +10° (*c* = 2, 0.1 N HCl).

L-Cyclohexylalanine Amide (3). To a slurry of L-phenylalanine amide (**9**) (15 g, 0.03 mol) in water (100 mL) was added wet 5% Rh on alumina (2.0 g, 20% wet with water), and the mixture was hydrogenated under hydrogen at 100 °C/250 psig for 18 h. The TLC (MeOH:H_2O, 8:2) of the reaction mixture showed the absence of **9**. The slurry was filtered hot through a 1-cm bed of Dicalite. The Dicalite bed was washed with hot water (20 mL). The filtrate and washings were combined and cooled to 5 °C. The precipitated solid was filtered, washed with water (20 mL), and dried in a vacuum oven at 50 °C/24 h to give 14.5 g (88%) of **3** as a white solid:[8] mp 112−115 °C; ^{1}H NMR ($CDCl_3$) δ 6.9−7.1 (br s, 1H, CONH), 5.7−5.9 (br s, 1H, CONH), 3.45 (dd, 1H, NH), 0.75−1.75 (br m, 15H, C_6H_{11}, CH_2, NH) Anal. Calcd for $C_9H_{18}N_2O$: C, 63.49; H, 10.63; N, 16.45. Found: C, 63.32; H, 10.56; N, 16.36.

This reaction was also preformed with 5.0 kg of substrate. The catalyst was Johnson Matthey 5% Rh−Al_2O_3 lot no. 021215001. The reaction was complete in just under 8 h. Work-up was analogous to the laboratory procedure.

Alternative Procedure. To a solution of **9** (10 g, 0.061 mol) in methanol (100 mL) was added 5% rhodium on alumina (1 g), and the mixture was hydrogenated under hydrogen at 80 °C/250 psi for 24 h. The TLC ($CHCl_3$:MeOH, 1:1) of the reaction mixture showed the absence of **9**. The mixture was filtered through a 1-cm bed of Celite. The Celite bed was washed with methanol (20 mL). The filtrate and washings were combined and concentrated to ~20 mL. Heptane (50 mL) was added and the mixture stirred and cooled to 10 °C for 2 h. The precipitated solid was filtered, washed with cold heptane (10 mL), and dried in a vacuum oven at 25 °C/24 h to give 7.5 g (72%) of **3** as a white solid which was identical to that obtained by the previous procedure.

L-Cyclohexylglycine (11). To a solution of L-phenylglycine (**10**) (10 g, 0.066 mol) in aqueous sodium hydroxide (1 N, 100 mL) was added Rh on alumina (0.75 g) and the mixture hydrogenated at 25 °C/160 psig for 24 h. The mixture was filtered through a 1-cm Dicalite bed. The bed was washed with water (30 mL). The filtrate and washings were combined, and the pH was adjusted to ~5.5 with 2 N hydrochloric acid. The precipitated solid was filtered, washed with water (2 × 100 mL), and dried in a vacuum oven at 50 °C to yield 11 g (98%) of L-cyclohexylglycine (**11**) as a white solid.

(8) Although **3** has been mentioned in the literature, no spectroscopic or characterization has been reported.

L-Cyclohexylalaninol(2): Direct Hydrogenation. To a solution of **12** (10 g, 0.066) in 2-propanol (50 mL) and concentrated hydrochloric acid (10 mL) was added rhodium on carbon (0.5 g, 5%, 65% wet) and the mixture hydrogenated at 60 °C/50 psig for 24 h. The TLC of the reaction mixture showed the absence of starting material. The reaction mixture was cooled to room temperature and filtered through a 1-cm Dicalite bed. The bed was washed with 2-propanol (20 mL). Concentration of the filtrate in vacuo gave 10 g (97%) of the amino alcohol **2** as its hydrochloride salt which was a white solid: mp 230 °C dec, $[\alpha]$ +2.6°(c = 1, MeOH).

Indirect Method: L-Boc-cyclohexylalaninol (14). To a solution of L-Boc-phenylalaninol (**13**) (10 g, 0.04 mol) in methanol (20 mL) was added rhodium on carbon (1 g, 5%, 65% wet with water) and the mixture hydrogenated at 60 °C/40−45 psig for 16 h. The TLC (MeOH:$CHCl_3$, 1:9) of the reaction mixture showed the absence of **13**. The mixture was cooled to room temperature and filtered through a 1-cm bed of Dicalite. The Dicalite bed was washed with methanol (10 mL). The filtrate and washings were concentrated to a colorless oil. This oil was dissolved in ethyl acetate (20 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated to give **14** as a colorless oil (9.4 g, 94%), $[\alpha]^{20}$ −25° (c = 1, ethanol).[5,9]

L-Cyclohexylalaninol (2). To a saturated solution of HCl in methanol (40 mL) was added **14** (10 g, 0.039 mol) in methanol (20 mL) over a period of 10 min. The reaction mixture was stirred at room temperature for 4 h and then concentrated to one-quarter of its original volume. The precipitated solid was filtered, washed with ether, and dried in a vacuum oven at room temperature to give **2** as its hydrochloride salt 6 g (75%): mp 230 °C dec.[10]

D-Boc-cyclohexylalaninol. To a solution of D-Boc-phenylalaninol (2 g, 0.008 mol) in methanol (10 mL) was added rhodium on carbon (0.2 g, 5%, 65% wet with water) and the mixture hydrogenated at 60 °C/40−45 psig for 16 h. The TLC of the reaction mixture showed the absence of starting material. The reaction was worked up as described above for the L-isomer to give the product as a colorless oil, **13** (1.95 g, 95%).

D-Cyclohexylalaninol Hydrochloride. The removal of the Boc group with methanolic HCl was performed as for the L-isomer to give the product as a white solid, mp 235 °C dec.

Received for review September 2, 2002.

OP0200773

(9) Luly, J. F.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487.
(10) Fournie-Zaluski, M. C.; Pascale, C.; Turcaud, S.; Bruetschy, L.; Lucas, E.; Noble, F.; Roques, B. P. *J. Med. Chem.* **1992**, *35*, 1259.