HETEROCYCLES, Vol. 71, No. 2, 2007, pp. 323 - 330. © The Japan Institute of Heterocyclic Chemistry
Received, 23rd October, 2006, Accepted, 19th December, 2006, Published online, 22nd December, 2006. COM-06-10926

PRACTICAL SYNTHESIS OF (-)-α-AMINOBENZOLACTAM *VIA* NITRATION-CYCLIZATION OF *L*-HOMOPHENYLALANINE ETHYL ESTER

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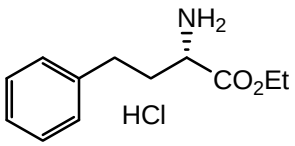
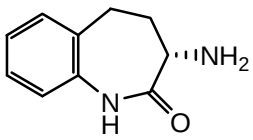
Abstract – A practical synthesis of chiral (-)-α-aminobenzolactam (**2**) is described. The target compound (**2)** was prepared from commercially available *L*-homophenylalanine ethyl ester hydrochloride (LHPE·HCl **1**) with a highly enantiomeric purity (>98% e.e.) by employing simple nitration and hydrogenation-cyclization reactions.

INTRODUCTION

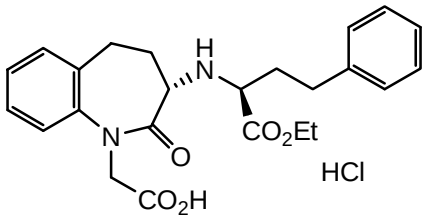
Optically active α-aminobenzolactam (**2**) is the key building blocks of many important biologically active compounds or drugs, such as anti-hypertensive drug benazepril·HCl (**3**),[1] antithrombotic agent (**4**)[2] and growth hormone secretagogue (GHS) (**5**)[3] (Figure 1).



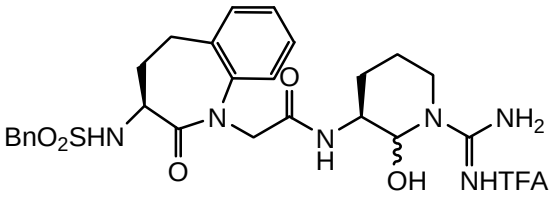
L-homophenylalanine ethyl ester hydrochloride (LHPE*i*¤HCl) (**1**)



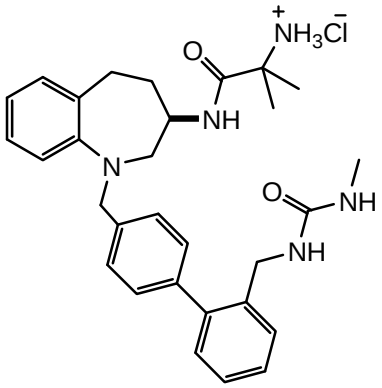
(-)-α-aminobenzolactam (**2**)



Benazepril.HCl (**3**)



antithrombotic agent (**4**)
benzo-fused CVS-1778



growth hormone secretagogue (**5**)
L-692428

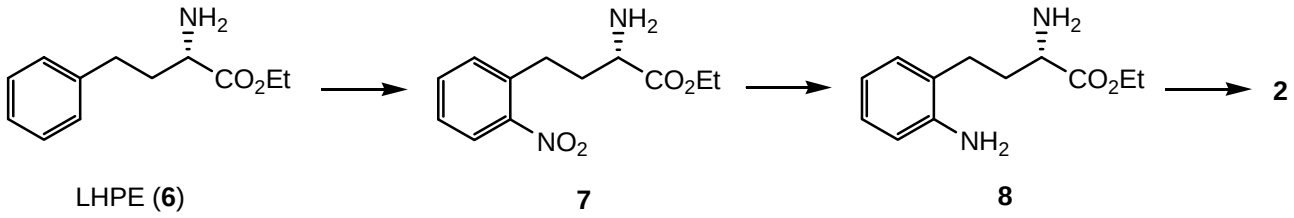
Figure 1

In the literatures, the synthesis of (-)-α-aminobenzolactam (**2**) was mostly prepared through resolution of racemic enantiomers[4] by fractional crystallization of the diastereomeric tartaric acid salts,[5] or enantioselective synthesis by employing asymmetric catalytic hydrogenation.[6] These methods usually suffered low yields, high cost, and tedious operations which made them unpractical for industrial use. The use of "chiral pool" for the synthesis of **2** was reported by Jackson who used an amino acid-derived organozinc reagent to react with 2-iodoaniline followed by cyclization and hydrogenation to prepare (-)-α-aminobenzolactam (**2**),[7] however, the overall yield was only 9%. Recently we reported an alternative approach to enantiopure (-)-α-aminobenzolactam (**2**) based on the oxidative-cyclization of the *N*-methoxyamide of LHPE·HCl (**1**) which gave a much better overall yield (35%).[8] Unfortunately, the use of expensive reagents in Chang's method such as iodomethane and [bis(trifluoroacetoxy)iodo]benzene (PIFA) was still an obstacle for industrial use. Herein, we reported a simple and economic methodology through nitration of LHPE (**6**), followed by hydrogenation and cyclization to produce (-)-α-aminobenzolactam (**2**) in good yield with high optical purity (>98% e.e.).

RESULTS AND DISCUSSION

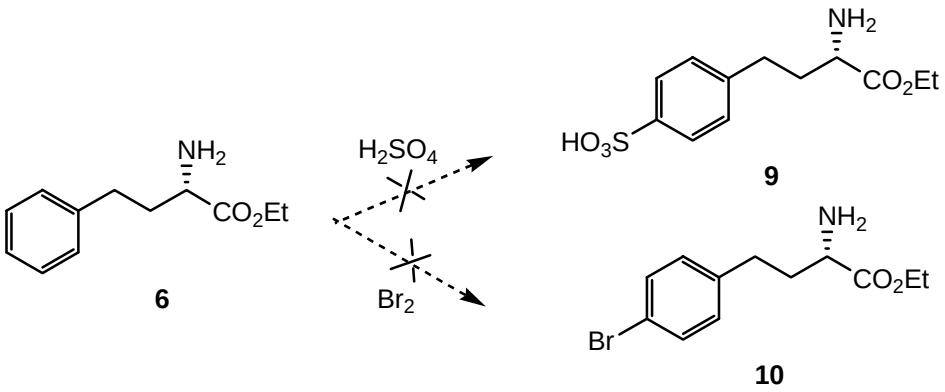
According to our synthetic protocol illustrated in Scheme 1, the major task is to obtain a high regioselectivity toward *o*-substitution product in the nitration reaction and a facial process in the separation of *ortho*- and *para*-substituted products. On the other hand, we found no racemization occurred

at the C2 chiral center through the whole process from LHPE to the target compound (**2**).



Scheme 1

In our early study, we tried to obtain only *ortho*-nitrated product by pre-occupation of *para*-position of LHPE (**6**) (or LHPE·HCl **1**) through the transformation of LHPE (**6**) into its sulfate compound (**9**) or brominated compound (**10**) (Scheme 2). However, the conversion of LHPE (**6**) to compound (**9**) was difficult due to the solubility problem. On the other hand, the bromination reaction occurred well but led to messy side products.



Scheme 2

The direct nitration of LHPE·HCl **(1**) was the only choice after we failed on the pre-occupation strategy of *para*-position of LHPE (**6**)**.** Various nitration reagents and conditions, such as HNO_3, Fuming HNO_3, HOAc/HNO_3 (1:2), Ac_2O/HNO_3 (1:2), HOAc/fuming HNO_3 (1:1) and Ac_2O/fuming HNO_3 (1:1), were tested on LHPE·HCl **(1**). Unfortunately, all of these methods resulted in vigorous reactions and formed messy products. Accidentally, we found the nitration for acetic acid salt of LHPE (**6**) led to the desired products in a much better yield than the hydrochloric acid salt (**1**) (Table 1). Therefore, we neutralized LHPE·HCl (**1**) to LHPE (**6**) by Na_2CO_3 with a yield of 99%. However, the free base from LHPE (**6**) was not so stable that would slowly form a dimeric lactam even at room temperature over a few days. Therefore, the amino group of LHPE (**6**) needed to be quickly converted into a stable salt by dissolving in an acid as the solvent for nitration reaction. We found that varying salts of LHPE (**6**) would lead to various products in the nitration reactions, as listed in Table 1.

Table 1. The Nitration of LHPE·H_2SO_4 and LHPE·HOAc

Entry	Substrate	Solvent	Nitration reagent[a]	*Ortho / Para*[b]	7+7' (%)[c]
1	LHPE·H_2SO_4	H_2SO_4	H_2SO_4+65%HNO_3 (1:2)	0.25	90%
2	LHPE·H_2SO_4	H_2SO_4	HOAc+65%HNO_3 (1:2)	no reaction	--
3	LHPE·H_2SO_4	H_2SO_4	Ac_2O+65%HNO_3 (1:1)	0.29	89%
4	LHPE·H_2SO_4	H_2SO_4	H_2SO_4+fumingHNO_3(1:2)	messy products	--
5	LHPE·H_2SO_4	H_2SO_4	HOAc+fumingHNO_3(1:1)	0.28	85%
6	LHPE·H_2SO_4	H_2SO_4	Ac_2O+fuming HNO_3 (1:2)	messy products	--
7	LHPE·HOAc	H_2SO_4	H_2SO_4+65%HNO_3 (1:2)	0.27	90%
8	LHPE·HOAc	HOAc	HOAc+65%HNO_3 (1:2)	no reaction	--
9	LHPE·HOAc	HOAc	Ac_2O+65%HNO_3 (1:1)	no reaction	--
10	LHPE·HOAc	HOAc	Ac_2O+65%HNO_3 (1:2)	0.33	67%
11	LHPE·HOAc	HOAc	H_2SO_4+fumingHNO_3(1:2)	messy products	--
12	LHPE·HOAc	HOAc	HOAc+fumingHNO_3(1:1)	incompletion	--
13	LHPE·HOAc	HOAc	Ac_2O+fumingHNO_3 (1:1)	0.35	77%
14	LHPE·HOAc	HOAc	Ac_2O+fumingHNO_3(1:2)	0.40	90%
15	LHPE·HOAc	HOAc	Ac_2O+fumingHNO_3(1:3)	0.36	86%
16	LHPE·HOAc	HOAc	HOAc+fumingHNO_3(1:2)	0.34	84%
17	LHPE·HOAc	HOAc	HOAc+fumingHNO_3(1:3)	0.30	76%

[a] The ratio of mixture nitration reagent was reported by ratios in volume (v/v).
[b] The ratio of *o*-nitrated compound (**7**) to *p*-nitrated compound (**7'**) was measured by gas chromatography.
[c] The combination yields of *para*- and *ortho*-nitrated compounds were determined by GC analysis of the crude products.

From Table 1, the nitration system of (Ac_2O/fuming HNO_3 in HOAc) (entry 14) gave the best yield and ratio of *o*-substitution product. Operationally, LHPE (**6**) first reacted with acetic acid to become LHPE·HOAc and then this salt was dissolved in acetic acid before the treatment of nitration agents. The nitration reagent, acetyl nitrate, was formed efficiently by simply mixing of nitric acid and acetic anhydride at ambient temperature.[9]

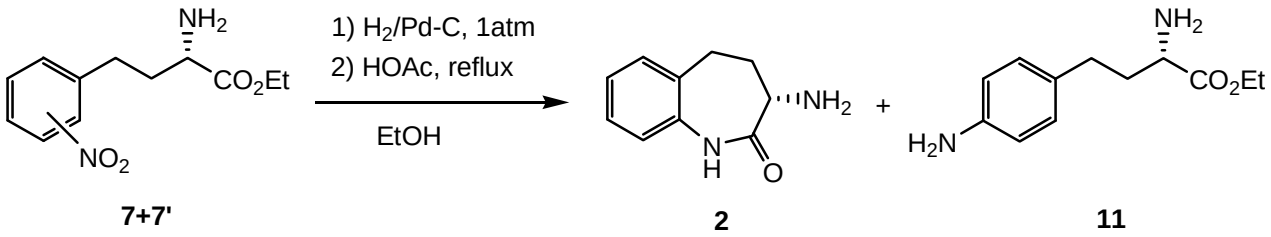
$$Ac_2O + HNO_3 \rightleftharpoons AcONO_2 + AcOH$$

Experiments indicated that the nitration reagent prepared from a 1:1 mixture of Ac_2O and HNO_3(65%) gave no nitration reaction for LHPE·HOAc (entry 9), but a low yield of nitration product (**7**) was obtained when we changed the ratio to 1:2 (entry 10). We also found that the concentration of nitric acid had a significant influence on the nitration. Our observations indicated that the nitration of LHPE (**6**) with reagents prepared from fuming HNO_3 and Ac_2O gave higher ratio of *o*-substitution than the other reagents

we used. In principle, the *o*-substitution product should be preferred due to kinetic reason while we use a highly reactive and small size electrophile, and the nitronium ion which is generated from Ac_2O and HNO_3 mixture is a very strong electrophile relatively. On the other hand, a similar hypothetic mechanism for *o*-substitution and solvent effects had been reported by Schofield.[10] However, the *p*-substitution product still remained as the major product in nitration due to steric effect.

From the economic view, the nitration system of (H_2SO_4 or H_2SO_4/HNO_3) should be selected (entry 1). But the whole reaction is not homogeneous, thus a suddenly occurred exothermal reaction would raise the reaction temperature and generated messy products. Our observation indicated that the nitration reaction at the temperatures higher than 40 ^oC would lead to messy side products. Thus, the reproducibility was poor in such reaction which prevents its usage in practical purpose (entry 1). As a result, the combination of HNO_3 with either acetic anhydride or acetic acid should be prefer for such nitration (entries 13~17) with the advantages of good solubility and mild exothermicity to give higher content of *o*-substitution product (**7**).

The nitrated products (**7**) and (**7'**) were hydrogenated by H_2 (1 atm)/Pd-C in ethanol at room temperature. After the nitro group was converted to amino group completely, Pd-C was filtered off and the resulting solution was refluxed for ten hours under the catalysis of HOAc to give the cyclized product (**2**) (Scheme 3).



Scheme 3

The final cyclized product (**2**) was obtained as a mixture with *para*-amino compound (**11**) after removing the ethanol. The separation of compounds (**2)** and (**11**) could be achieved by simple extraction through the selective hydrolysis of ester (**11**) by 30% NaOH aqueous solution into its corresponding acid. The cyclized product (**2**) could be extracted by ethyl acetate while *p*-substitution compound (**11**) and the other side products retained in the alkali aqueous layer. HPLC analysis showed that no ring open reaction occurred on compound (**2**) through the whole separation process. After recrystallization, optically pure (-)-α-aminobenzolactam (**2**) was successfully obtained with a highly enantiomeric purity (> 98% e.e) and an overall yield of 30% (from LHPE **6**). In addition, the compound (**11**) could be extracted after

acidifying the aqueous solution, and its re-use in synthesis of (-)-α-aminobenzolactam (**2**) is currently under investigation.

In summary, we have reported an efficient synthesis of (-)-α-aminobenzolactam (**2**) by employing commercially available *L*-homophenylalanine ethyl ester hydrochloride (LHPE·HCl **1**) as the chiral source. The target compound (**2**) was successfully prepared with retained chirality at C2 through nitration of the benzene ring, reduction of nitro group by hydrogenation, and acid catalyzed cyclization reaction. This process presented a very economic way to transform *L*-homophenylalanine ethyl ester hydrochloride into (-)-α-aminobenzolactam (**2**) in an overall yield of 30% with >98% e.e.

EXPERIMENTAL

Starting materials were obtained from commercial suppliers and used without further purification unless otherwise stated. Gas chromatography was carried out using SHIMADZU 2010 and HPLC using SHIMADZU SPD-10A. Melting points are uncorrected. Optical rotations were measured on a Perkins–Elmer 241 polarimeter. Infrared spectra were recorded on a Hitachi 270-30 infrared spectrophotometer. NMR spectra were recorded on a Varian Mercury 400 or Varian Inova 600. The chemical shifts are reported as δ value in ppm relative to TMS ($\delta = 0$), which was used as the internal standard in $CDCl_3$ for ^1H NMR spectra and the center peak of $CDCl_3$ (δ = 77.0 ppm), which was used as the internal standard in ^{13}C NMR spectra. Elemental analyses were collected on a Foss Heraeus CHN-O-Rapid elemental analyzer.

L-Homophenylalanine ethyl ester (LHPE 6):

To a stirring solution of H_2O (180 mL) and Na_2CO_3 (13.10 g, 123.60 mmol) was added EtOAc (100 mL), then LHPE·HCl (**1**) (40.18 g, 164.85 mmol) was slowly added into the mixture at temperature between 20~30 ^oC. The organic layer was separated and concentrated to give 33.50 g of LHPE (**2**) as a colorless liquid in 98 % yield. $[\alpha]_D$ = +39.1 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.33 (m, 5H, PhH), 4.18 (q, *J* = 7.1, 2H, OCH_2), 3.40-3.55 (br, 2H, CH), 2.76 (t, *J* = 7.0, 2H, $PhCH_2$), 2.15-2.40 (br, 2H, NH_2), 2.05-2.20 (m, 1H, CH_2), 1.85-2.00 (m, 1H, CH_2), 1.29(t, *J* = 7.1, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 141.1, 128.2, 128.1, 125.7, 60.5, 53.7, 36.2, 31.7, 14.0.

Nitration reaction procedure:

To a flask contained HOAc (35 mL) was added slowly LHPE (**2**) (33.12 g, 159.79 mmol) and kept stirring until the resulting salt (LHPE·HOAc) was dissolved. The solution was then cooled in an ice bath and was added dropwise the cold (0 ^oC) mixture of Ac_2O/fuming HNO_3 (30 mL + 30 mL) while the reaction temperature was controlled below 10°C. After addition, the mixture was stirred at the same

temperature for 0.5 hr and the completion of the nitration reaction was checked by GC. The resulting solution was neutralized with saturated aqueous $NaHCO_3$ until pH 8 and was directly extracted with CH_2Cl_2 (100 mL x 3). The combined organic solution was washed with 100 mL of water, dried over $MgSO_4$, and concentrated in vacuum to give the 40.40 g of nitro compounds (a mixture of *o*-, *p*-, *m*-nitrated compounds and other side products) as a brownish oil with a ratio of 1:1.50 (*o*-nitrated compound : *p*-nitrated compound, by GC), and the total yield of *o*-nitrated and *p*-nitrated compounds was 90% that was determined by GC chromatography analysis. Other nitration reactions were carried out in similar way but using different nitration systems, the results are showed in Table 1.

(-)-α-Aminobenzolactam (2):

To a solution of nitrated compound (a mixture of 40.00 g *of o*-, *p*-, *m*-nitrated compounds from the nitration reaction) in EtOH (200 mL) was added 5% Pd-C (18.00 g). The resulting mixture was bubbled with a slow stream of hydrogen and the mixture was hydrogenated under atmosphere of hydrogen for 1 h at ambient temperature. After the GC chromatography indicated the completion of reaction, Pd-C was filtered off and the solution was used directly for the next cyclization reaction without purification. Additional EtOH (400 mL) and HOAc (35 mL) were added and the resulting solution was refluxed for 10 h and the completion of the reaction was checked by GC. After evaporation of the solvent, the residual oil was dissolved in 200 mL of 30% aqueous NaOH solution to adjust the pH to above 11, and then the basic solution was extracted with EtOAc (100 mL x 5). The combined organic layers were added HCl until pH 6~7 and a yellowish solid appeared. After the solid was collected by filteration, stirred with 100 mL of 7% Na_2CO_3 aqueous solution and extracted with EtOAc (200 mL x 2). The organic layer was concentrated in vacuum to give (-)-α-aminobenzolactam (**2**) [(3*S*)-3-amino-1,3,4,5-tetrahydrobenzo[*b*]azepin-2-one] (8.45 g) as a white solid in a total yield of 30% (from LHPE **6**) with e.e.> 98 % based on the HPLC analysis with chiral column (Daicel, CROWNPAK CR(+)); $[\alpha]_D = -447.0$ (*c* 1.02, CH_3OH) [lit.,[7] $[\alpha]_D = -446.0$ (*c* 1.0, CH_3OH)]; mp 151–152 °C (lit.,[7] mp 147–149°C); ^{1}H NMR (400 MHz, CD_3OD) δ 7.31–7.25 (m, 2H, ArH), 7.21–7.15 (m, 1H, ArH), 7.10 (d, *J* = 8.0 Hz, 1H, ArH), 3.47–3.42 (m, 1H, C<u>H</u>NH_2), 2.92–2.86 (m, 1H, $ArCH_2$), 2.75–2.69 (m, 1H, $ArCH_2$), 2.58–2.45 (m, 1H, CH_2), 2.05–1.95 (m, 1H, CH_2); ^{13}C NMR (150 MHz, CD_3OD) δ 177.0, 139.1, 136.3, 131.3, 129.4, 127.9, 124.2, 52.5, 39.6, 30.3; Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.09; H, 6.84; N, 15.84.

REFERENCE

1. (a) J. W. H. Watthey, J. L. Stanton, M. Desai, J. E. Babiarz, and B. M. Finn, *J. Med. Chem.*, 1985, **28**, 1511. (b) S. K. Boyer, R. A. Pfund, R. E. Portmann, G. H. Sedelmeier, and H. F. Wetter, *Helv. Chim.*

Acta, 1988, **71**, 337. (c) L. T. Yu, J. L. Huang, C. Y. Chang, and T. K. Yang, *Molecules*, 2006, **11**, 641.

2. (a) S. Y. Tamura, E. A. Goldman, P. W. Bergum, and J. E. Semple, *Bioorg. Med. Chem. Lett*., 1999**,** **9**, 2573. (b) J. Z. Ho, T. S. Gibson, and J. E. Semple, *ibid*., 2002, **12**, 743.
3. N. Zheng, J. D. Armstrong, K. K. Eng, J. Keller, T. Liu, R. Purick, J. Lynch, F. W. Hartner, and R. P. Volante, *Tetrahedron: Asymmetry*, 2003, **14**, 3435.
4. W. Lin, X. Zhang, Z. He, Y. Jin, L. Gong, and A. Mi, *Synth. Commun.,* 2002, **32**, 3279.
5. (a) N. G. Anderson, *Org. Process Res. Develop.,* 2005, **9**, 800. (b) W. R. Schoen, J. M. Pisano, K. Prendergast, Jr., M. J. Wyvratt, M. H. Fischer, K. Chen, W. S. Wanda, B. Butler, R. G. Smith, and R. G. Ball, *J. Med. Chem.,* 1994, **37**, 897.
6. J. D. Armstrong, III, K. K. Eng, J. L. Keller, R. M. Purick, Jr., F. W.Hartner, W. B. Choi, D. Askin, and R. P. Volante, *Tetrahedron Lett*., 1994, **35**, 3239.
7. R. F. W. Jackson, R. J. Moore, and C. S. Dexter, *J. Org. Chem*., 1998, **63**, 7875.
8. C. Y. Chang and T. K. Yang, *Tetrahedron: Asymmetry*, 2003, **14**, 2081.
9. (a) F. G. Bordwell and E. W. Garbisch, *J. Am. Chem. Soc.,* 1960, **82**, 3588. (b) O. Mantsch, N. Bodor, and F. Hodorsan, *Rev. Chim. (Roumania)*, 1968, **13**, 1435.
10. K. Schofield, *Aromatic Nitration*, Published by the Press of Syndicate of the University of Cambridge, 1980, p.61.