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Synthesis of *N*-Boc-(*R*)-α-phenyl-γ-aminobutyric acid using an in situ diastereoselective protonation strategy

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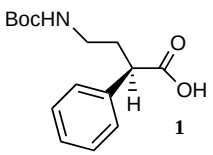
Abstract—The synthesis of (±)-*N*-phthalyl α-phenyl-γ-aminobutyric acid and its asymmetric transformation via ketene formation have been investigated, allowing, after hydrolysis and amine protection, the preparation of the enantiomerically pure *N*-Boc-(*R*)-α-phenyl-γ-aminobutyric acid. © 2002 Published by Elsevier Science Ltd.

1. Introduction

γ-Aminobutyric acid (GABA) is an important inhibitory neurotransmitter in the central nervous system[1] and its derivatives, in particular those analogues bearing a phenyl group in the α, β or γ position, have received much attention.[2]

We have previously described an efficient asymmetric transformation of racemic carboxylic acids involving a prochiral ketene which is well adapted to the synthesis of optically active α-aryl-substituted compounds.[3] Extending our investigations, we now wish to report our results concerning the asymmetric synthesis of *N*-Boc-(*R*)-α-phenyl-γ-aminobutyric acid **1**.



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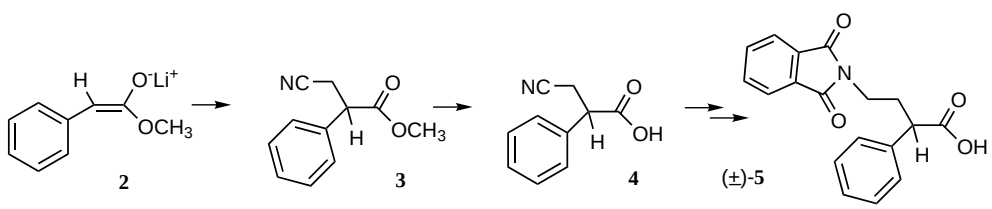
2. Results and discussion

The synthesis of compound **1** consists of: (a) the preparation of the racemic γ-amino acid with the amine function totally protected by a phthalimido group (Scheme 1); (b) transformation of the acid function into the corresponding acyl chloride followed by the stereoselective addition of a chiral alcohol to the prochiral ketene generated in situ (Scheme 2); (c) the acid-hydrolysis of both the ester and the amine protecting group followed by Boc protection of the amino group to yield the optically active *N*-Boc-γ-amino acid derivative (Scheme 2).

Cyanomethylation of the enolate of methyl phenyl acetate (formed at low temperature using lithium hexamethyldisilazide) with bromoacetonitrile, followed by saponification of the methyl ester **3** afforded the cyano acid **4** in good yield. Reduction of the cyano group with lithium triethylborohydride[4] gave the corresponding racemic γ-amino acid in moderate yield, which was then



2 **3** **4** (±)-**5**

Scheme 1. Synthesis of racemic *N*-phthalyl α-phenyl-γ-aminobutyric acid.

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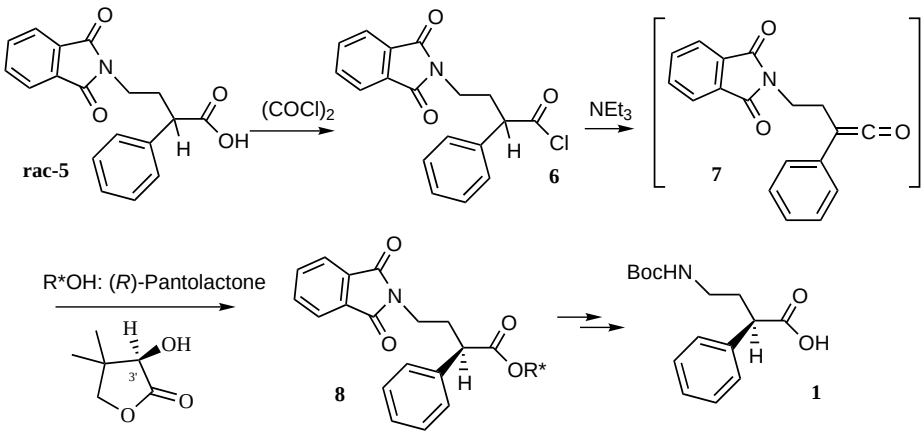

Scheme 2. Stereoselective synthesis of (*R*)-*N*-Boc protected α-phenyl-γ-aminobutyric acid.

directly converted to the target *N*-phthalyl derivative (±)-**5** (Scheme 1).

The key step in this asymmetric synthesis, i.e. ketene formation and chiral alcohol addition was completed using a one-pot procedure (Scheme 2). The best result was obtained when the ketene **7** was formed in situ by treatment of the acyl chloride **6** at room temperature with 1.2 equiv. of triethylamine over 15 min. Subsequent addition of (*R*)-pantolactone at the same temperature afforded the corresponding pantolactonyl ester **8** in good yield (75%) as an 85/15 diastereoisomeric mixture. When the generation time of the ketene at room temperature was higher than 15 min, we observed both lower yield and stereoselectivity. Proton NMR analysis after trapping the ketene with CH_3OD indicated that beside the corresponding Cα deuterated methyl ester, side products are formed (probably resulting from polymerization of the ketene). No improvement in the stereoselectivity or yield resulted from the use of either lower temperature or a different tertiary amine.

Moreover, it should be noted that different attempts to directly transform the racemic cyano acid **4** into the corresponding enantiomerically enriched ester by the same procedure, always afforded the corresponding racemic pantolactonyl 3-cyano-2-phenyl propionic ester.

The diastereomerically pure (*R*,*R*)-*N*-phthalyl pantolactonyl ester **8** could be obtained after meticulous column chromatography on silica gel. Several crystallization attempts failed. The diastereoisomeric excess (d.e.) of **8** was determined for the crude product from the ^{1}H NMR spectra ($CDCl_3$) by integration of the methyl signal of the pantolactonyl moiety of the two diastereoisomers.

Hydrolysis of the diastereoisomerically pure (*R*,*R*)-**8** under acidic conditions afforded the corresponding (*R*)-γ-amino acid hydrochloride, which was directly converted into its *N*-Boc derivative **1** using di-*tert*-butyldicarbonate. The (*R*)-configuration was assigned by comparison of the specific rotation of **1** with literature data[2d] indicating that the (*R*,*R*)-ester was mainly formed during this asymmetric transformation process.

3. Experimental

Tetrahydrofuran (THF) was freshly distilled under argon from sodium and benzophenone; triethylamine (NEt_3) was distilled from KOH and ninhydrin. Thin-layer chromatography (tlc) was carried out on silica gel (60 F_{254}, Merck 5715) and spots located with UV light or iodine vapors. All other chemicals were commercially pure compounds and were used as received. Melting points were determined with a Büchi apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer, 241 polarimeter. HPLC analysis were performed on a Waters 510 instrument with a variable detector using a reverse phase nucleosil C_{18}, 5 μm (250×10 mm), flow: 1 mL/min, H_2O/CH_3CN/0.1% TFA gradient 0–100% (15 min). ^{1}H NMR spectra were recorded on a Bruker AC 250 or Bruker A DRX 400 spectrometers. Data are reported as follows: chemical shifts (δ) in ppm with respect to TMS, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (J) in Hz. The ESI mass spectra were recorded with a platform II quadrupole mass spectrometer (Micromass, Manchester, UK) fitted with an electrospray source.

3.1. Phenylacetic acid methyl ester 2

The phenylacetic methyl ester **2** was prepared from phenyl acetic acid (4.08 g, 30.0 mmol), thionyl chloride and methanol as previously described in the literature[5] (4.27 g, 28.5 mmol, 95% yield). It was obtained as a colorless oil; tlc (eluent hexane/diethyl ether 1/1) R_f = 0.75; ^{1}H NMR ($CDCl_3$) δ = 3.64 (s, 2H, $C_6H_5CH_2CO$), 3.70 (s, 3H, OCH_3), 7.31 (m, 5H, *H*-phenyl).

3.2. 3-Cyano-2-phenyl propionic acid methyl ester 3

A solution of *n*-butyllithium (2.5 M) in hexane (8.7 mL, 22.0 mmol) was added dropwise over 5 min to a stirred

solution of hexamethyldisilazane (4.8 mL, 24.0 mmol) in dry THF (45 mL) at −78°C under argon and the mixture was stirred for 1 h at −78°C. A solution of **2** (3.0 g, 20.0 mmol) in THF (27 mL) was then added over 10 min, keeping the temperature below −78°C during the addition. After stirring the mixture for 1 h at −78°C, bromoacetonitrile (2.4 mL, 36.0 mmol) was added dropwise in dry THF (27 mL) at the same temperature. The mixture was stirred for an additional 1 h at −78°C, and then warmed slowly to room temperature. After stirring at room temperature for 16 h, the reaction mixture was quenched with 1N aqueous HCl (100 mL) and THF was removed at reduced pressure. The aqueous layer was extracted with diethyl ether (3×150 mL) and the combined extracts were washed with water, dried and concentrated at reduced pressure. Column chromatography on silica gel, eluting with diethyl ether/hexane (1/1, R_f=0.39), yielded the pure compound **3** as a white solid (2.9 g, 15.4 mmol, 77% yield). Mp 53–54°C; HPLC: rt 10.75 min; ^{1}H NMR ($CDCl_3$) δ=2.80 (dd, J=7.6 Hz and J=16.8 Hz, 1H, HC*H*-CN), 3.03 (dd, J=7.6 Hz and J=16.8 Hz, 1H, HC*H*-CN), 3.71 (s, 3H, OCH_3), 3.94 (t, $J_1=J_2$=7.6 Hz, 1H, C*H*-CO_2CH_3), 7.27 (m, 2H, *H*-phenyl), 7.36 (m, 3H, *H*-phenyl).

3.3. (±)-3-Cyano-2-phenylpropionic acid 4

To a solution of compound **3** (2.27 g, 12.0 mmol) in ethanol (80 mL) was added at room temperature a 1N sodium hydroxide solution (18 mL, 1.5 equiv.). The mixture was stirred until disappearance of the starting material (about 4 h, monitoring the reaction by tlc). The volatile products were distilled at reduced pressure. Water (60 mL) was added to the residue and the mixture was washed with ethyl acetate (100 mL). Then, the aqueous solution was acidified with a 1N HCl solution (pH 2–3) and extracted with ethyl acetate (3×100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated at reduced pressure to afford the expected compound **4** as a white solid (1.94 g, 11.1 mmol, 93% yield). Mp 87–88°C; HPLC: rt 8.56 min; ^{1}H NMR ($CDCl_3$) δ=2.82 (dd, J=7.5 Hz and J=16.8 Hz, 1H, HC*H*-CN), 3.04 (dd, J=7.5 Hz and J=16.8 Hz, 1H, HC*H*-CN), 4.03 (t, $J_1=J_2$=7.5 Hz, 1H, C*H*-CO_2H), 7.30 (m, 2H, *H*-phenyl), 7.40 (m, 3H, *H*-phenyl).

3.4. *N*-Phthalyl-(±)-4-amino-2-phenylbutyric acid 5

To a vigorously stirred solution of compound **4** (1.75 g, 10 mmol) in THF (30 mL) at 0°C was added slowly a THF solution of lithium triethylborohydride (1 M, 20 mL, 2 equiv.). After stirring at room temperature for 20 h, the reaction mixture was slowly neutralized with dilute hydrochloric acid (pH 4–5) with ice-cooling. The mixture was stirred for 1 h at room temperature and THF was evaporated at reduced pressure. The resulting aqueous phase was washed with ethyl acetate before concentration at reduced pressure. To the oily-solid residue was added 2 equiv. of triethylamine (2.8 mL) in toluene (100 mL) and the reaction mixture was heated under reflux for 4 h while water was removed by azeotropic distillation (Dean–Stark). Phthalic anhydride (1.5 equiv.) was then added and the reaction mixture was heated under reflux for 5 h (the formed water was removed as described previously). After elimination of the volatile products at reduced pressure, a 1N HCl solution (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (3×100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated at reduced pressure. Flash column chromatography on silica gel of the crude compound, eluting with ethyl acetate/hexane (1/1, R_f=0.18), yielded the pure compound **5** as a white solid (0.77 g, 2.5 mmol, 25% yield). Mp 140–141°C; HPLC: rt 11.02 min; ^{1}H NMR (DMSO-d_6) δ=2.01 (m, 1H, HC*H*-CH_2NPht), 2.35 (m, 1H, HC*H*-CH_2NPht), 3.60 (m, 3H, C*H*-CO_2H and CH_2-NPht), 7.26 (m, 5H, *H*-phenyl), 7.84 (m, 4H, *H*-phthalyl); MS (ESI) m/z: 292.1, 310.0 [(M+H)$^+$], 263.9, 641.4 [(2M+Na)$^+$].

3.5. *N*-Phthalyl-(±)-4-amino-2-phenylbutyric acid chloride 6

A mixture of *N*-phthalyl-(±)-4-amino-2-phenylbutyric acid **5** (1 equiv.) and oxalyl chloride (10 equiv.) was stirred under argon at 35°C for 12 h. Evaporation of oxalyl chloride excess yielded the corresponding *N*-phthalyl-(±)-4-amino-2-phenylbutyric acid chloride **6**, which was used without further purification in the following step.

3.6. *N*-Phthalyl-3-amino-2-phenylbutyric acid pantolactonyl ester 8

To a stirred solution of *N*-phthalyl-(±)-4-amino-2-phenylbutyric acid chloride **6** (1.0 mmol) in anhydrous THF (5 mL) cooled to 0°C and under argon, was added NEt_3 (0.17 mL, 1.2 equiv.) in THF (0.5 mL). After 15 min stirring at room temperature, a solution of (*R*)-pantolactone (0.13 g, 1 equiv.) in THF (0.5 mL) was added. The mixture was stirred for 16 h at room temperature, then 1N aqueous HCl solution (5 mL) was added at 0°C and the mixture was extracted with ethyl acetate (3×10 mL). After concentration of the combined organic extracts at reduced pressure, a column chromatography on silica gel, eluting with ethyl acetate/hexane (1/1, R_f=0.62), yielded the pure compound **8** as a colorless oil (0.31 g, 75% yield, 70% d.e.). A second column chromatography on silica gel eluting with CH_2Cl_2/ethyl acetate (10/0.4, R_f=0.55) yielded optically pure (*R*,*R*)-**8** as a colorless oil (0.19 g, 45% yield, >99% d.e.). HPLC: rt 13.13 min; $[\alpha]_D^{20}=-21$ (c=1.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ=0.98 (s, 3H, 4′-CH_3), 1.10 (s, 3H, 4′-CH_3), 2.26 (m, 1H, HC*H*-CH_2N), 2.43 (m, 1H, HC*H*-CH_2N), 3.69 (m, 3H, C*H*-C_6H_5 and CH_2N), 3.89 (d, J=9 Hz, 1H, 5′-HC*H*), 3.93 (d, J=9 Hz, 1H, 5′-HC*H*), 5.24 (s, 1H, 3′-C*H*), 7.13 (m, 1H, *H*-phenyl), 7.23 (m, 4H, *H*-phenyl), 7.62 (m, 2H, *H*-phthalyl), 7.72 (m, 2H, *H*-phthalyl); ^{13}C NMR ($CDCl_3$) δ 18.78 (*C*H$_3$), 21.96 (*C*H$_3$), 30.30 (*C*H$_2$-CH_2N), 35.08 (*C*H$_2$N), 39.14 (*C*(CH$_3$)$_2$), 48.16 (*C*H-C_6H_5), 74.36 (C-3′), 75.12 (*C*-5′), 122.18 (*C*H-phthalyl), 126.65, 126.97, 127.71 (*C*H-phenyl), 130.97 (*C*-phthalyl), 132.92 (*C*H-phthalyl), 135.90 (*C*-phenyl),

167.18, 170.69, 170.88 (*C*O); MS (ESI) *m*/*z*: 292.0, 422.0 [(M+H)$^+$], 444.0 [(M+Na)$^+$], 865.2 [(2M+Na)$^+$]. Anal. calcd for $C_{24}H_{23}NO_6$: C, 68.40; H, 5.50; N, 3.32%. Found: C, 67.86; H, 5.70; N, 3.10%.

The minor diastereoisomer (*S*,*R*)-**8** has the following NMR physical data:[6,7] ^{1}H NMR ($CDCl_3$) $\delta = 0.60$ (s, 3H, 4′-CH_3), 0.87 (s, 3H, 4′-CH_3), 2.26 (m, 1H, HC*H*-CH_2N), 2.43 (m, 1H, HC*H*-CH_2N), 3.69 (m, 3H, C*H*-C_6H_5 and CH_2N), 3.84 (s, 2H, 5′-CH_2), 5.25 (s, 1H, 3′-C*H*), 7.13 (m, 1H, *H*-phenyl), 7.23 (m, 4H, *H*-phenyl), 7.62 (m, 2H, *H*-phthalyl), 7.72 (m, 2H, *H*-phthalyl); ^{13}C NMR ($CDCl_3$) δ 18.20 (*C*H_3), 21.78 (*C*H_3), 29.81 (*C*H_2-CH_2N), 34.81 (*C*H_2N), 39.41 (*C*(CH_3)$_2$), 47.83 (*C*H-C_6H_5), 74.00 (C-3′), 75.04 (*C*-5′), 122.18 (*C*H-phthalyl), 126.71, 126.97, 127.27 (*C*H-phenyl), 127.81 (*C*-phthalyl), 132.86 (*C*H-phthalyl), 136.54 (*C*-phenyl), 167.16, 170.87, 171.25 (*C*O).

3.7. *N*-Boc-(*R*)-3-amino-2-phenylbutyric acid (*R*)-1

A mixture of the *N*-phthalyl pantolactonyl ester (*R*,*R*)-**8** (100 mg, 0.24 mmol), acetic acid (0.66 mL) and a 6N HCl solution (6.65 mL) was heated under reflux until completion of the hydrolysis (4 h–5 h), the reaction being monitored by tlc. The mixture was allowed to warm to room temperature and the volatile products were distilled at reduced pressure. To a solution of the residue in dioxane/H_2O (2/1, 10 mL) at 0°C was added sodium hydroxide (1 equiv.) and di-*tert*-butyldicarbonate (57 mg, 1.1 equiv.). After stirring the mixture for 12 h at room temperature the dioxane was evaporated at reduced pressure and water was added (10 mL). The resulting aqueous phase was successively washed with ethyl acetate (3×15 mL), acidified with 1N aqueous HCl solution (pH 2–3) and extracted with CH_2Cl_2 (3×15 mL). The combined CH_2Cl_2 extracts were dried over Na_2SO_4 and concentrated at reduced pressure to afford the expected compound *N*-Boc-(*R*)-3-amino-2-phenylbutyric acid **1** as a colorless solid (39 mg, 59% yield). Mp 98–100°C; $[\alpha]_D^{20} = -67$ ($c = 0.6$, CH_2Cl_2); HPLC: rt 19.19 min; ^{1}H NMR ($CDCl_3$) $\delta = 1.42$ (s, 9H, C(CH_3)$_3$), 1.94 (m, 1H, HC*H*-CH_2N), 2.30 (m, 1H, HC*H*-CH_2N), 3.12 (m, 2H, CH_2N), 3.62 (t, $J_1 = J_2 = 7$ Hz,, 1H, C*H*), 4.61 and 6.13 (br, 1H, N*H*Boc), 7.31 (m, 5H, *H*-phenyl); MS (ESI) *m*/*z*: 223.9, 280.1 [(M+H)$^+$], 302.1 [(M+Na)$^+$], 559.3 [(2M+H)$^+$], 581.2 [(2M+Na)$^+$].

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6. NMR data for compound **8** deduced from comparison of the data of the racemic mixture and the enantiomerically pure compound obtained.
7. To obtain a diastereoisomeric mixture of the pantolactonyl ester **8**, (±)-**5** was esterified with (*R*)-pantolactone in the presence of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) (96% yield, (*R*,*R*)/(*R*,*S*): 45/55).