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# A CONVENIENT SYNTHESIS OF 3-ETHOXYCARBONYLAMINO-2-HYDROXY-4-PHENYLBUTYRIC ACID

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## A CONVENIENT SYNTHESIS OF 3-ETHOXYCARBONYLAMINO-2-HYDROXY-4-PHENYLBUTYRIC ACID

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3-Amino-2-hydroxy-4-phenylbutyric acid (AHPBA) and its derivatives<sup>1</sup> are useful starting materials for the preparation of HIV-1 protease inhibitors such as saquinavir<sup>2</sup> and amprenavir.<sup>3</sup> Various synthetic routes for the preparation of this type of compounds have been published.<sup>4-6</sup> We previously reported a novel and facile synthetic route to AHPBA and its derivatives (4*S*,5*S*)-4-benzyl-5-hydroxymethyl oxazolidin-2-one as part of our study of the synthesis of HIV-1 protease inhibitors.<sup>7</sup> In this paper, *N*-phthaloyl protected *L*-phenylalanine was treated with

### **OPPI BRIEFS**

thionyl chloride followed by hydrogenation of the acyl chloride on Pd/C, giving 2-phthalimido-3-phenylpropionaldehyde. The aldehyde reacted with Nagata's reagent to afford 3-phthalimido-2-hydroxy-4-phenylbutyronitrile as a diastereomeric mixture. After hydrolysis, the cyanohydrin was transformed into ( $2S_3S$ )-6. The overall yield of this route was 12% from phenylalanine.



Reagents and conditions: a) NaBH<sub>4</sub>/I<sub>2</sub>, THF, reflux, 20 h; b) phthalic anhydride, 140-150°C, 10mm Hg or reflux in toluene; c) Py•SO<sub>3</sub>, DMSO, NEt<sub>3</sub>(cat), CH<sub>2</sub>Cl<sub>2</sub>; d) CH<sub>3</sub>NO<sub>2</sub> and NEt<sub>3</sub> in THF at -40°C for 4 h then at r.t. overnight; e) HCl (concentrated), reflux, 24 h; then addition NaOH (40%) and ClCO<sub>2</sub>Et dropwise alternately while the pH was kept at 7-8

The present communication reports an improved and convenient method for preparation of the key intermediate 3-ethoxycarbonylamino-2-hydroxy-4-phenylbutyric acid. (*R*)-phenylalanine 1 was reduced to (*R*)-phenylalaninol 2 with sodium borohydride/iodine reductive system in THF in 78% yield.<sup>8</sup> Protection the 2-amino alcohol 2 by heating with phthalic anhydride in toluene afforded (*R*)-2-phthaloyl amino-3-phenyl-1-propanol 3 in 82% yield. (*R*)-2-Phthalimido-3-phenylpropionaldehyde 4 was obtained in 65% by oxidation the phthaloyl protected 2-amino alcohol 3 with sulfur trioxide-pyridine complex (Py•SO<sub>3</sub>).<sup>9,10</sup> The crude product was used without further purification. Treatment of the aldehyde 4 with nitromethane in the presence of NEt<sub>3</sub> as catalyst (Henry reaction) at  $-40^{\circ}$ C to r.t.<sup>11</sup> gave (2*R*S,3*R*)-2-hydroxy-4-phenyl-3phthaloylamino-1-nitrobutane 5a and 5b as a mixture in a ratio of 5.2:1;<sup>12</sup> the (2*R*,3*R*)-diastereomeric isomer 5a was purified by recrystallization. Compound 5a was refluxed in conc. hydrochloric acid for 24 h; after filtration to remove insoluble material, the filtrate was alternately treated with NaOH (40%) and ethyl chloroformate dropwise while the pH was kept at 7-8 to afford (2*R*,3*R*)-3-ethoxycarbonylamino-2-hydroxy-4-phenylbutyric acid 6.

In summary, we have developed a convenient and effective synthetic method for preparation of 3-ethoxycarbonylamino-2-hydroxy-4-phenylbutyric acid in 18% overall yield from phenylalanine.

### **EXPERIMENTAL SECTION**

Melting points were measured on a Buchi 510 apparatus and were uncorrected. Elemental analyses were performed on a Elementar Vario EL instrument. Infrared spectra were obtained on

a Nicolet Magna 750 spectrometer. NMR spectra were measured on Bruker AMX-400 spectrometer with tetramethylsilane as internal standard. Specific rotations were measured on a Perkin-Elmer 241 MC. Mass spectra were determined on a Varian MAT-95 mass spectrometer.

(*R*)-Phenylalaninol (2).- Sodium borohydride (6.6 g, 0.17 mol) was suspended in THF (100 mL) and the mixture was cooled in an ice bath, then (*R*)-phenylalanine (12 g, 73 mmol) was added in one portion to the mixture on stirring. A solution of iodine (18.44 g, 73 mmol) in THF (100 mL) was added to this mixture dropwise under nitrogen atmosphere. After addition, the solution was refluxed overnight. After cooling to r.t., methanol was added to the mixture dropwise until gas evolution ceased. The solvent was removed and the residue was stirred in 20% KOH (100 mL) for 4 h at r.t. The aqueous phase was extracted with dichloromethane (150 mL x 3). The combined organic layers were washed with water and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvent, the crude material was recrystallized twice from toluene affording **2** as a white solid (8.61 g, 78%), mp. 91-93°C, *lit.*<sup>8</sup> mp. 92-94°C. <sup>1</sup>HNMR (CDCl<sub>3</sub>):  $\delta$  7.2~7.4 (m, 5H), 3.6 (dd, *J* = 3.9, 6.6Hz, 1H), 3.4 (dd, *J* = 3.9, 6.6 Hz, 1H), 3.1 (m, 1H), 2.8 (dd, *J* = 5.1, 8.4, Hz, 1H), 2.5 (dd, *J* = 5.1, 8.4, 1H), 1.7 (s, 3H).

(*R*)-2-Phthaloylamino-3-phenyl-1-propanol (3).- (*R*)-Phenylalaninol (3.44 g, 22.8 mmol) and phthalic anhydride (3.71 g, 25 mmol) were placed into a flask (100 mL) and the mixture was heated to 140-150°C *in vacuo* (less than 10 mm Hg) with stirring for 6 h. After cooling to r.t., a white solid was obtained. The crude material was recrystallized from ethyl acetate/petroleum ether giving **3** as a white solid (5.25 g, 82%), mp. 102-104°C. <sup>1</sup>HNMR (CDCl<sub>3</sub>):  $\delta$  7.6~7.8 (m, 5H), 7.2 (m, 4H), 4.6 (m, 1H), 4.1 (dd, *J* = 7.0, 4.9 Hz, 1H), 3.9 (dd, *J* = 3.4, 8.5 Hz, 1H), 3.2 (d, *J* = 8.2 Hz, 2H), 2.2 (broad, 1H); EI-MS m/z(%): 281 (M<sup>+</sup>, 24), 263 (6), 250 (44), 232 (48), 190 (100), 172 (72), 91 (42), 77 (36); IR (KBr, cm<sup>-1</sup>): 3453.9, 1770.4, 1697.1, 1405.9, 1087.7, 873.6, 719.3;

Anal. Calcd for C<sub>17</sub>H<sub>15</sub>NO<sub>3</sub>: C, 72.59; H, 5.34; N, 4.98. Found: C,72.55; H, 5.27; N, 4.81

(*R*)-2-Phthalimido-3-phenylpropionaldehyde (4).- (*R*)-2-Phthaloylamino-3-phenyl-1-propanol (1 g, 3.6 mmmol) and NEt<sub>3</sub> (6.6 mL) were dissolved in DMSO/CH<sub>2</sub>Cl<sub>2</sub> (20 mL, V/V = 1/1) then cooled in an ice bath; a solution of Py•SO<sub>3</sub> (2.49 g, 15.7 mmmol) in DMSO/CH<sub>2</sub>Cl<sub>2</sub> (20 mL, V/V = 1/1) was added dropwise to the amino alcohol **3** solution. After the addition, the mixture was left to stand at r.t. for 1.5 h with stirring. Water (30 mL) was added, and the mixture was extracted with ether (100 mL x 3). The organic layers were washed with 5% citric acid (10 mL x 2), brine (10 mL x 2), and water (10 mL x 2). The extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the aldehyde **4** as a yellow oil, which solidified through the addition of petroleum ether to its dichloromethane solution. The crude solid was recrystallized from dichloromethane/ petroleum ether to give white solid (0.64 g, 65%), mp. 107-110°C, *lit.*<sup>13</sup> mp. 110-113°C.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  9.8 (s, 1H), 7.10~7.20 (m, 5H), 7.70 (m, 2H), 7.80 (m, 2H), 5.0 (dd, J = 5.5, 10.7 Hz, 1H), 3.60 (dd, J = 5.5, 14.1 Hz, 2H), 3.30 (dd, J = 10.7, 14.1 Hz, 2H); EI-MS m/z(%): 279 (M<sup>+</sup>, 8), 251 (100), 232 (88), 91 (56).

**2-Hydroxy-4-phenyl-3-phthaloylamino-1-nitrobutane** (5a/5b).- Aldehyde 4 (4 g, 14.3 mmol) was dissolved in THF (60 mL) and cooled to  $-40^{\circ}$ C; nitromethane (16 mL, 0.29 mmol) and NEt<sub>3</sub> (0.4 mL) were added and the mixture was kept at  $-40^{\circ}$ C for 4 h then r.t. overnight. HCl (4 mL, V/V = 1/4) was added to stop the reaction which was then concentrated *in vacuo*. To the residue was added water (30 mL), and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL x 3). The combined organic layers were washed with brine (10 mL x 3) and water (10 mL x 3), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and evaporated *in vacuo* to afford the crude product as a white solid, which was recrystallized from dichloromethane/ petroleum ether to afford (±)-(2*R*,3*R*)-2-hydroxy-4-phenyl-3-phthaloylamino-1-nitrobutane (5a) as the main product. White solid (2.46 g, 51 %); mp. 186-188°C.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.6~7.8 (m, 4H), 7.2 (m, 5H), 4.9 (broad, 1H), 4.6 (m, 1H), 4.4 (m, 2H), 3.7 (s, 1H), 3.3 (dd, J = 8.0 Hz, 2H); EI-MS m/z(%): 340 (M<sup>+</sup>), 310 (8), 250 (100), 232 (64), 160 (52), 91 (66), 77 (40); IR (KBr, cm<sup>-1</sup>): 3540.7, 1737.6, 1766.5, 1700.9, 1522.4, 1386.6, 1087.7, 725.1, 702.0, 530.3.

Anal. Calcd for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>: C, 63.53; H, 4.71; N, 8.24. Found: C, 63.54; H, 4.77; N, 7.96

(±)-(2S,3R)-2-Hydroxy-4-phenyl-3-phthaloylamino-1-nitrobutane (5b) was obtained through the column chromatography (dichloromethane/ petroleum ether = 1/3) of the mother liquor of 5a as white solid (0.46 g, 10 %); mp. 140-141°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.7~7.8 (m, 4H), 7.2 (m, 5H), 4.6 (m, 2H), 4.3 (m, 2H), 3.2 (d, *J* = 8.0 Hz, 2H), 1.5 (s, 1H); EI-MS m/z(%): 340 (M<sup>+</sup>), 310 (4), 250 (100), 232 (52), 160 (28), 91 (40), 77 (20); IR (KBr, cm<sup>-1</sup>): 3465.5, 1776.1, 1708.6, 1548.6, 1388.5, 1091.5, 721.3, 530.3.

Anal. Calcd for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>: C, 63.53; H, 4.71; N, 8.24. Found: C, 63.37; H, 4.91; N, 8.06

(±)-(2*R*,3*R*)- 3-Ethoxycarbonylamino-2-hydroxy-4-phenylbutyric acid (6).- Nitroaldol adduct 5a (0.3 g, 0.88 mmol) was suspended in 25% HCl (30 mL) and refluxed for 24 h. The reaction mixture was then cooled to 0°C and stirred for 2 h. After filtration, the filtrate was adjusted to pH 7-8 with 40% aqueous solution of NaOH. To the solution was added ethyl chloroformate (0.2 mL, 2.17 mmol) and 40% aqueous solution of NaOH alternately to maintain the pH value of the reaction mixture at 7-8. The mixture was stirred at r.t. for an additional 2 h, then adjusted to pH 1 with concentrated hydrochloric acid. The mixture was extracted with ethyl acetate (20 mL x 3). The organic layer was washed with water and dried over anhydrous MgSO<sub>4</sub>. Removal of the solvent gave a yellow oil which was crystallized from toluene to afford 6 (0.20 g, 85%) as a white crystal. mp. 138-139°C, *lit.*<sup>14</sup> mp. 138-140°C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  7.0~7.3 (m, 5H), 3.6~4.0 (m, 4H), 2.65 (d, J = 6.9 Hz, 2H), 1.0 (t, J = 7.2 Hz, 3H).

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