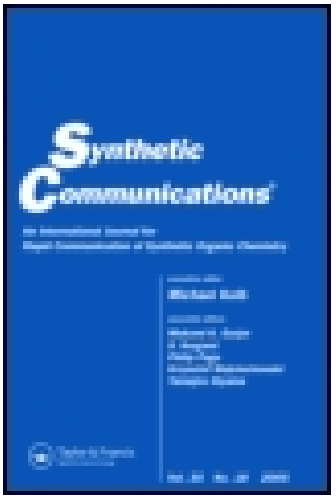

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Preparation of (RS)-5-Amino-3-carboxypentanoic Acid (1)

Sajid Malik [a] & Peter B. Wyatt [a]

[a] Department of Chemistry , Queen Mary and Westfield College, University of London , Mile End Road, London, El 4NS, UK

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PREPARATION OF (*RS*)-5-AMINO-3-CARBOXYPENTANOIC ACID (**1**)

Sajid Malik and Peter B. Wyatt*

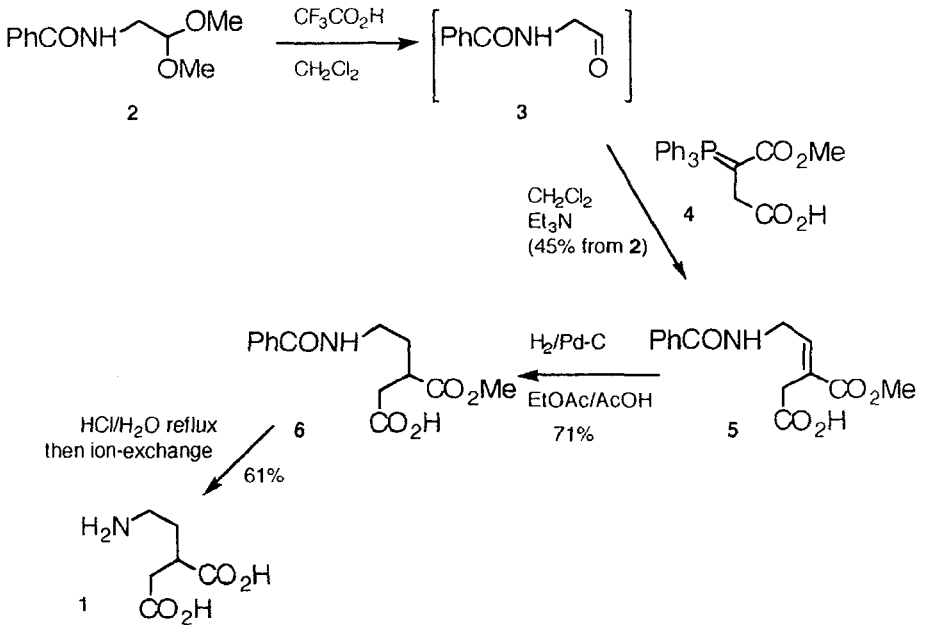
Department of Chemistry, Queen Mary and Westfield College, University of London, Mile End Road, London E1 4NS, UK.

Abstract: (*RS*)-5-Amino-3-carboxypentanoic acid (**1**) was prepared by a Wittig reaction of *N*-benzoylglycinal (**3**) with the phosphorane (**4**), followed by catalytic hydrogenation and acid hydrolysis.

Glutamic, aspartic and γ-aminobutyric acids are all neurotransmitters and many related substances have neurological activity.[1] We now report the preparation of (*RS*)-5-amino-3-carboxypentanoic acid (**1**), which is currently under biological investigation. The preparation of the amino acid (**1**) has previously been claimed,[2] via the alkylation of the triethyl ester of carboxybutanedioic acid with *N*-(2-bromoethyl)phthalimide followed by deprotection and decarboxylation under vigorous conditions (conc. hydrochloric acid, sealed tube, 170 °C). However, no yields or characterisation data were given. We chose to prepare (*RS*)-5-amino-3-carboxypentanoic acid (**1**) by an alternative route, which proved to be very convenient (see Scheme).

* To whom correspondence should be addressed.

SCHEME



Treatment of 2-(benzamido)acetaldehyde dimethyl acetal (**2**) with trifluoroacetic acid gave *N*-benzoylglycinal (**3**), which underwent a Wittig reaction with the phosphorane (**4**) in the presence of triethylamine to give the crystalline (*E*)-alkene (**5**). The double bond geometry was indicated by the existence of a nuclear Overhauser effect between the two methylene groups. Hydrogenation over a palladium catalyst gave the protected amino acid (**6**). Deprotection with refluxing hydrochloric acid, followed by purification by ion exchange chromatography and crystallisation afforded (*RS*)-5-amino-3-carboxypentanoic acid (**1**).

EXPERIMENTAL

(E)-5-*Benzamido-3-(methoxycarbonyl)pent-3-enoic acid.* (**5**).- 2-(Benzamido)acetaldehyde dimethyl acetal[3] (**2**) (6.17 g, 29.5 mmol) was dissolved in a mixture of CH_2Cl_2 (20 cm^3) and CF_3CO_2H (20 cm^3) and kept at 20 °C for 50 min. The solvents were then evaporated and the residue was redissolved in CH_2Cl_2 (35 cm^3) and treated with methyl 2-(triphenylphosphoranylidene)-butanedioate[4,5] (**4**) (13.89 g, 35.4 mmol), then the solution was basified (pH 9-10 to moist indicator paper) using anhydrous Et_3N. The solution was kept at room temperature for 3 d, then extracted with saturated aqueous $NaHCO_3$ (3 x 120 cm^3). The combined aqueous extracts were then acidified to pH 3 using 1 M H_2SO_4, saturated with NaCl and extracted with EtOAc (3 x 120 cm^3). The combined EtOAc extracts were dried ($MgSO_4$) and concentrated to a small volume. Addition of petrol (bp 40-60 °C) caused (E)-5-*benzamido*-3-*(methoxycarbonyl)pent*-3-*enoic acid* (**5**) (2.98 g) to crystallise as large white prisms. Flash chromatography of the mother liquor [EtOAc-$CHCl_3$ (1:1) to EtOAc; gradient elution] allowed further crystals of (**5**) (0.69 g) to be obtained. Thus the total yield of the title compound (**5**) was (3.67 g, 45%), with the following properties: mp 94-96 °C (Found: C, 60.38; H, 5.39; N, 4.74. $C_{14}H_{15}NO_5$ requires C, 60.65; H, 5.45; N, 5.05 %); δ_H (250 MHz; $CDCl_3$) 3.54 (2 H, s, CH_2CO_2H), 3.78 (3 H, s, CO_2Me), 4.24 (2 H, dd, *J* 7 and 6 Hz, CH_2N), 6.73 (1 H, br t, *J*6 Hz, NH), 7.02 (1 H, t, *J* 7 Hz, olefinic-H), 7.38-7.54 (3 H, m, Ph 3-, 4- and 5-H) and 7.78 (2 H, dd, *J* 7 and 2 Hz, Ph 2- and 6-H), irradiation at CH_2CO_2H gave a 4% nOe at CH_2N whereas irradiation at CH_2N gave a 3% nOe at CH_2CO_2H; *m/z* (EI) 277 (M^+, 30%) and 77 (100%).

(RS)-5-*benzamido*-3-(*methoxycarbonyl*)*pentanoic acid* (**6**).- (*E*)-5-benzamido-3-(methoxycarbonyl)pent-3-enoic acid (**5**) (1.00 g, 3.61 mmol) was dissolved in a mixture of EtOAc (15 cm^3) and AcOH (5 cm^3), then shaken with 5% Pd on C (0.43 g) under H_2 (2 Bar) in a Parr hydrogenator for 2 d. Filtration (Celite®), evaporation and trituration with Et_2O (40 cm^3) afforded (RS)-5-*benzamido*-3-(*methoxycarbonyl*)*pentanoic acid* (**6**) (0.72 g, 71%) as a white solid, mp 114-116 ^0C (from $CHCl_3$) (Found: C, 60.00; H, 6.23; N, 4.91. $C_{14}H_{17}NO_5$ requires C, 60.21; H, 6.13; N, 5.01); δ_H (250 MHz; $CDCl_3$) 1.85-2.09 (2 H, m, NCH_2CH_2), 2.60 (1 H, dd, *J* 17 and 6 Hz, $CHCO_2H$), 2.85 (1 H, dd, *J* 17 and 7.5 Hz, $CHCO_2H$), 2.91-3.02 (1 H, m, $CHCO_2Me$), 3.39-3.67 (2 H, m, NCH_2), 3.70 (3 H, s, CO_2Me), 6.57 (1 H, br t, *J* 6 Hz, NH), 7.39-7.55 (3 H, m, Ph 3-, 4- and 5-H) and 7.77 (2 H, dd, *J* 7 and 2 Hz, Ph 2- and 6-H); *m/z* (EI) 280 (MH^+, 5%) and 77 (100%).

(RS)-5-*Amino*-3-*carboxypentanoic acid* (**1**).- (*RS*)-5-Benzamido-3-(methoxycarbonyl)pentanoic acid (**6**) (1.32 g, 4.76 mmol) was refluxed in concentrated hydrochloric acid (20 cm^3) for 60 h. The mixture was then evaporated *in vacuo* and the residue was evaporated three times from water, dissolved in water (20 cm^3) and washed with Et_2O (3 x 20 cm^3). The aqueous extract was concentrated and applied to a column of Dowex® 50X2-100 ion exchange resin (H^+ form), which was eluted first with water and then with 0.9 M aqueous ammonia. The ninhydrin-positive fractions were pooled, evaporated and rechromatographed on a column of Amberlite® IR400 (AcO^- form), which was eluted with a gradient from water to 10% (v/v) aqueous AcOH. Pooling and evaporation of the ninhydrin-positive fractions, followed by recrystallisation from

aqueous ethanol, gave (RS)-5-*Amino*-3-*carboxypentanoic acid* (**1**) (0.47 g, 61%) as white crystals, mp 173-175 °C (Found: C, 44.51; H, 6.75; N, 8.50. $C_6H_{11}NO_4$ requires C, 44.72; H, 6.88; N, 8.69%); $\nu_{max.}$ (KBr)/cm^{-1} 3300-2500, 1718 and 1636; δ_H (250 MHz; D_2O) 1.82-2.06 (2 H, m,NCH_2CH_2), 2.52 (1 H, dd, *J* 17 and 6 Hz, $CHCO_2H$), 2.68 (1 H, dd, *J* 17 and 8 Hz, $CHCO_2H$), 2.72-2.86 (1 H, m, $CHCO_2H$) and 3.14 (2 H, t, *J* 7.5 Hz, NCH_2); δ_C (63 MHz; D_2O) 31.95, 40.61, 44.08, 180.83 and 183.46; *m/z* (FAB) 162 (MH^+, 100%).

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