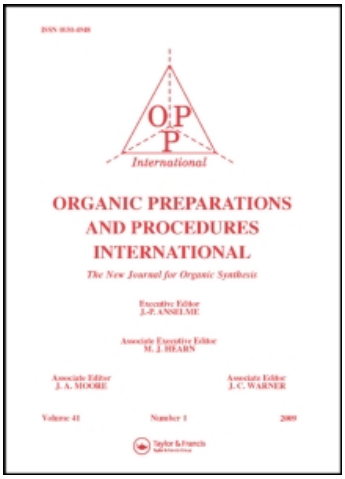

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A PRACTICAL SYNTHESIS OF ETHYL L-GLUTAMINE (L-Theanine)

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A PRACTICAL SYNTHESIS OF ETHYL L-GLUTAMINE

(L-Theanine)

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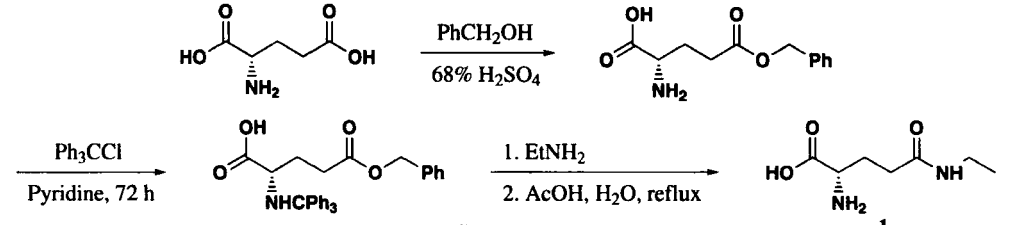
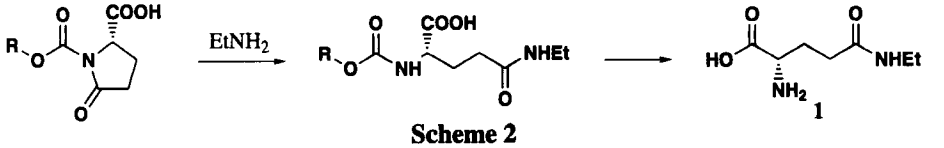
L-Theanine (**1**) is a unique free form amino acid found in the tea plant and in the mushrooms Xerocomus badius and certain species of genus *Camellia*, *C. japonica* and *C. sasanqua*. It increases α-waves-producing mental and physical relaxation and decreases stress and anxiety without drowsiness.[1] Studies suggest that L-theanine may also find other applications such as controlling hypertension,[2] improving learning performance,[3] heightening mental acuity, promoting concentration, acting antagonistically against the paralysis induced by caffeine,[4] supporting the immune system, lowering blood pressure, and increasing brain dopamine levels; there are no known side-effects.[5-7]

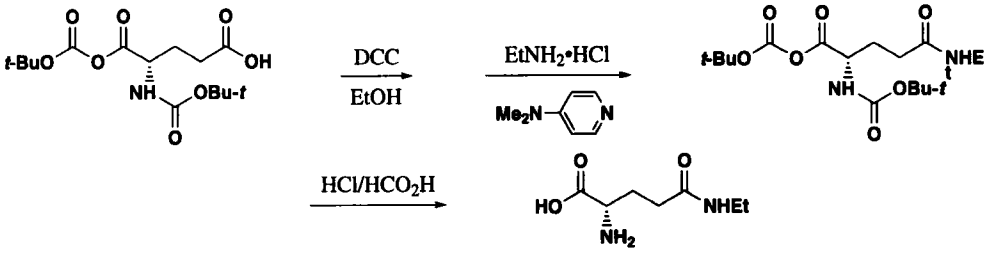
As part of our research program, we required an efficient method to prepare L-theanine. Surprisingly however, a review of the literature, including patents, indicated the absence a practical synthesis. A summary of the known procedures[8-12] is shown in *Schemes 1*,[13] *2*[14] and *3*.[15]



Scheme 1

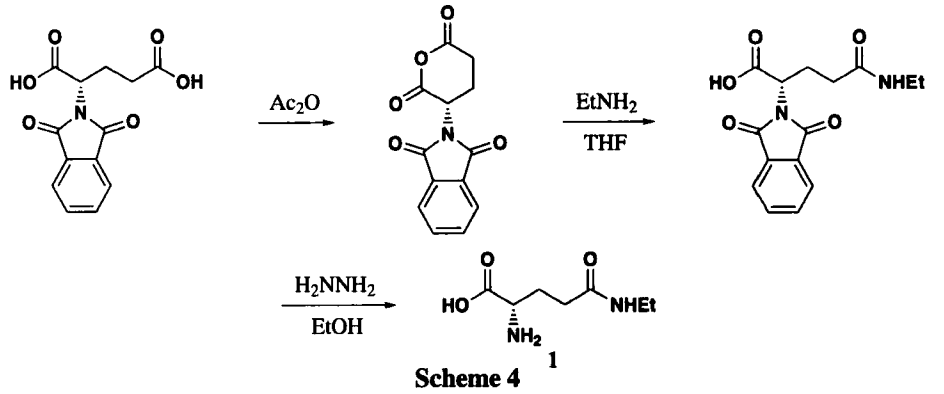


Scheme 2



Scheme 3

These schemes utilized either expensive or non-trivial reagents and involve rather lengthy multi-step procedures. However, an examination of other references revealed the possibility of the utilization of N-phthaloyl-L-glutamic anhydride for L-glutamylations. The earlier reports[16,17] suggested that dehydration of commercially available N-phthaloyl-L-glutamic acid with acetic anhydride, followed by amidation with ethylamine and deprotection with hydrazine might provide the desired L-theanine through a simple procedure. Indeed, we report a simple one-pot synthesis of L-theanine as shown in *Scheme 4*.



Scheme 4

EXPERIMENTAL SECTION

Mps. were determined on an electrically heated Thomas-Hoover capillary melting point apparatus and are uncorrected. N-Phthaloyl-L-glutamic acid was purchased from Fluka (Cat # 79840). All other chemicals were reagent grade, obtained from other sources. ^{1}H-NMR spectra were recorded on a Bruker 400(400MHz). Chemical shifts are expressed in δ values downfield from DSS, used as internal standard.

Ethyl L-Glutamine (L-Theanine).- In a 1 L flask, a mixture of N-phthaloyl-L-glutamic acid (100 g, 0.36 mol) and freshly distilled acetic anhydride (200 mL) was heated at 100°C until solution was complete and then stirred for an additional 5 min at 100°C. The solution was cooled and concentrated *in vacuo*, and the resulting solid was washed with cold acetic anhydride and dry ether and then dried *in vacuo*. After the addition of anhydrous tetrahydrofuran (500 mL) to the residue, ethylamine (22.5 g, 0.5 mol) was added slowly over 1 hour, and the mixture was stirred for additional 16 h at RT. Evaporation of excess ethylamine and tetrahydrofuran under reduced pressure gave a solid to which absolute ethanol (500 mL) and hydrazine hydrate (15 mL, 85%) were added. The mixture was heated to reflux for 4 h, and the solvent was evaporated under reduced pressure. Water (100 mL) was added to the flask, and the mixture was heated to reflux for 30 min. After cooling, it was filtered by suction and acetone (800 mL) was added to the cooled (to room temperature) filtrate. The white precipitate which resulted was collected, washed with acetone, recrystallized from 80% ethanol and dried in vacuum for 2 h to give 43.8 g (70%) of white crystals, mp. 212-214°C, *lit.*[13] 214-216°C. IR (KBr): 3442, 3296, 2971, 1645, 1584 cm^{-1}. ^{1}HNMR (D_2O): δ 3.75 (t, 1H), 3.19 (q, 2H), 2.15-2.39 (m, 4H),1.10 (t, 3H). $[\alpha]_D^{20}$ = + 8.6°C (c = 1.00, H_2O), *lit.*[13] $[\alpha]_D^{20}$ = +8.6 (c = 1.00, H_2O).

Anal. Calcd for $C_7H_{14}N_2O_3$: C, 48.28; H, 8.05; N, 16.09. Found: C, 48.22; H, 8.00; N, 16.01

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A FACILE AND DIRECT SYNTHESIS OF ALENDRONATE FROM PYRROLIDONE

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Alendronate (Fosamax), 4-amino-1-hydroxybutylidenebisphosphonic acid (alendronic acid) monosodium, is an anti-resorption agent used for the prevention and treatment of osteoporosis and for the prevention of osteoporotic fractures in postmenopausal women.[1] Various methods for the preparation of alendronic acid have been disclosed. In most of these methods, it was obtained from the reaction of γ-aminobutyric acid with phosphorous acid and phosphorous trichloride in such solvents as chlorobenzene,[2] methanesulfonic acid,[3] polyalkylene(glycol)[4] and methanesulfonic anhydride.[5] Alendronic acid can also be synthesized by 4-phthalimidobutanoyl