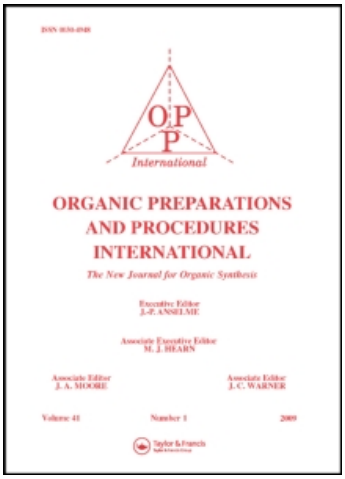

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A PRACTICAL PREPARATION OF *N,N,*-PHTHALYL-L-GLUTAMIC 1,5-ANHYDRIDE

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matography (hexane:EtOAc, 9:1) to afford pure **8** (0.79 g, 76%) as a pale yellow oil. ^{1}H NMR: (400MHz,$CDCl_3$): δ 5.05 (s, 1H, olefin), 2.23 (s, 1H, CH), 3.83 (s, 6H, CH_3O), 3.71 (s, 6H, CH_3O?2), 3.22 (d, J = 6.4Hz, 2H, CH_2), 2.06 (s, 3H, CH_3), 2.00 (s, 2H, CH_2), 1.97 (s, 2H, CH_2), 1.60 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.23 (s, 3H, CH_3). GC-MS (m/z): 364 (M^+, 95), 365 (M^+ + 1H, 20), 247 (50), 225 (100), 189 (50), 173 (20), 85 (22)

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.90. Found: C, 69.45; H, 8.82

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A PRACTICAL PREPARATION OF *N,N*-PHTHALYL-L-GLUTAMIC 1,5-ANHYDRIDE

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(08/13/04)

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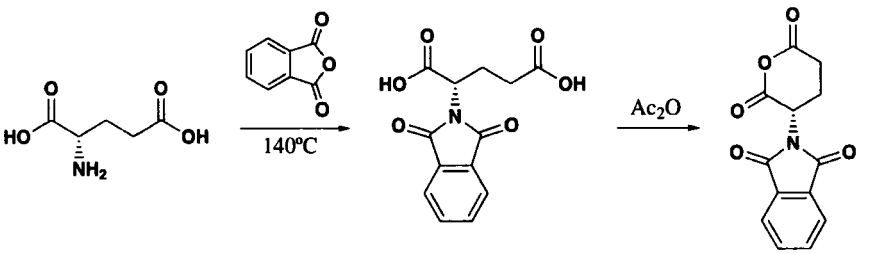
N,N-Phthalyl-L-glutamic anhydride is a crucial reagent for γ-glutamylations. A useful synthetic route to glutamylaminoacids and glutamylamino peptides has been successfully established by the utilization of compounds protected by the phthalyl group.[1] The phthalyl moiety was chosen in preference to the carbobenzoxy as a protecting group because ring opening of the appropriate L-glutamic anhydride with amines is known[2] to give γ-glutamyl derivatives with the former protecting group, while yielding α-glutamyl products with the latter.

In general, phthalimidoacids have been prepared by heating mixtures of the aminoacids and phthalic anhydride slightly above the fusion point of the anhydride,[3] but the product thus obtained from L-glutamic acid was not pure when crystallized from water.[4] The condensation

was then attempted in turn in presence of solvents, acetic acid, pyridine, and in order to ensure cyclization of the initially formed phthalamic acid, the solvent was evaporated and the residue was warmed with acetic anhydride. As expected, glutamic anhydride ring-closure also occurred, but was accompanied by racemization presumably at the phthalamic acid stage, the product being phthalyl-DL-glutamic anhydride. Racemization was avoided by carrying out the synthesis under milder conditions using diethyl L-glutamate[5] in place of the free aminoacid. The required ester was obtained from its hydrochloride by neutralization with anhydrous diethylamine, and on treatment of an etheral solution with phthalic anhydride diethyl *N*-(2-carboxybenzoyl)-L-glutamate was formed rapidly. Cyclization to diethyl phthalyl-L-glutamate was effected either by refluxing with ethanolic hydrogen chloride and distillation, or by reaction with cold thionyl chloride followed by heating the mixture in benzene. A modified procedure was reported with improved yield and quality.[6]

However, these procedures involve lengthy sequences and use complex protection and deprotection strategy. We sought a simple and reliable methodology to synthesize the *N,N*-phthalyl-L-glutamic 1,5-Anhydride (**1**) using glutamic acid and phthalic anhydride directly in good optical purity and yield.



Scheme 1 **1**

Our main goal was to devise a direct preparation of the phthalyl-L-acid which avoids the lengthy procedure. We found the conditions previously used for the direct preparation were too harsh to retain the optical active form and we used milder conditions for the preparation of phthalamic acid in order to keep the chiral center untouched; however, the reaction was incomplete under these conditions. We thus needed a good purification procedure to ensure the quality of final product and a brief report of the synthesis of γ-L-glutamyl-α-naphthylamine[7] helped toward the solution of this problem. The reaction of glutamic acid and phthalic anhydride at lower temperature (140°C), careful dehydration with acetic anhydride at 105°C and final recrystalization from xylene afforded the optical active product in good overall yield.

EXPERIMENTAL SECTION

Mps. were determined on an electrically heated Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker 400 (400MHz) instrument using $CDCl_3$ as the solvent with TMS as internal standard. Infrared spectra were obtained on a Bruker Vector-22 instrument. All chemicals are normal reagent grade obtainable.

***N,N*-Phthalyl-L-glutamic 1,5-Anhydride (1).**- Phthalic anhydride (148 g, 1 mol) was mixed with L-glutamic acid (147 g, 1 mol) and ground together in a mortar. The mixture was transferred to a three-necked flask, stirred and heated in an oil bath at 140°C until an oily mixture resulted; stirring was continued for a further 20 min. The colorless oil was cooled to 105°C, acetic anhydride (180 mL, 1.9 mol) was added, mixed completely and kept at 105°C for 20 min with stirring until it became a clear solution. Then 500 mL of xylene was added with stirring, cooled to 0°C and allowed to stand overnight. The precipitated colorless crystals were collected and washed with anhydrous ethanol to remove residual xylene. After drying *in vacuo* (desiccator) over anhydrous calcium chloride, the desired product (**1**) weighed 129.5 g (50% yield), mp. 194-196°C, *lit.*[6] 194-197°C. IR: (KBr): 1840, 1800, 1730, 725cm^{-1}. ^{1}H NMR: ($CDCl_3$): δ 2.51 (m, 4 H, CH_2), 5.13 (m, 1H, CH), 8.03 (m, 4H, CH). $[\alpha]_D^{20}$= –44.7°C (c 3, dioxane), *lit*[8] $[\alpha]_D^{22}$= –43.1°C (c 3, dioxane).

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