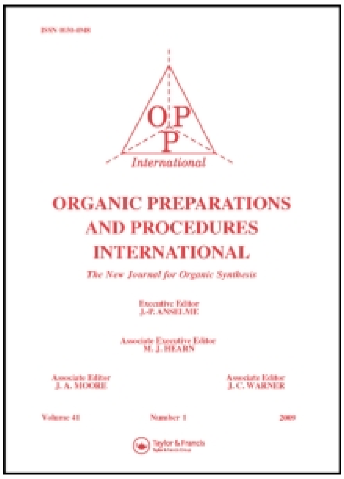

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IMPROVED SYNTHESIS OF SOME o-BSTERS OF N-PKOTECTED L-GLUTAMIC ACID

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IMPROVED SYNTHESIS OF SOME α-ESTERS OF N-PROTECTED L-GLUTAMIC ACID

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α-*t*-Butyl ester of N-benzyloxycarbonyl-L-glutamic acid (Z-Glu-OtBu) and α-benzyl ester of N-butyloxycarbonyl-L-glutamic acid (Boc-Glu-OBzl) serve as key substrates in the synthesis of γ-glutamyl peptides. Z-Glu-OtBu has been obtained from Z-Glu(OMe)-OH by *t*-butylation with *t*-butyl acetate[1] or isobutylene[2] followed by alkaline hydrolysis of the γ-methyl ester. In the first case, the *t*-butylation requires four days and large volumes of acetate and the yield is 86%. The second reaction uses gaseous reagent and needs about three days and gave a 79% yield of product. We now describe a simpler method which affords slightly higher yields of Z-Glu-OtBu, using $POCl_3$ and *t*-BuOH in pyridine;[3] this method is particularly convenient for large scale preparations.

$$\text{Z-Glu(OMe)-OH} + POCl_3 + \underline{t}\text{-BuOH} + 2C_5H_5N \longrightarrow$$

$$\text{Z-Glu(OMe)O}\underline{t}\text{Bu} + C_5H_5N\cdot HOPOCl_2 + C_5H_5N\cdot HCl$$

Boc-Glu-OBzl had previously been obtained either through ring-opening the intramolecular anhydride ($\text{Boc-G}\underbrace{\text{lu-O}}$) with benzyl alcohol[4,5] or through direct esterification with benzyl bromide.[6,7] In both cases, the product was isolated from the reaction mixture as its dicyclohexylammonium salt,[4-7] which was then cleaved with citric acid. The previous methods (especially the first) are multi-step procedures and thus time-consuming. The overall yields, based on Boc-Glu by the first method are reported to be 28%,[4] 52%[4] and 47%[5] (the difference in yields comes from the mode of synthesis of Boc-Glu-O) and by the second to be 28%.[7] We also describe an improvement in the isolation of the product. After direct esterification, Boc-Glu(OBzl)-OBzl and Boc-Glu are removed by the appropriate extractions. The first compound is left in the organic layer (A, see Experimental Section) and the second one is removed from the organic layer (B) by washing with 0.02N K_2CO_3. This procedure made the use of dicyclohexylamine unnecessary and resulted in a higher yield of product of higher purity.

EXPERIMENTAL SECTION

t-BuOH was dried as follows: 2 L of alcohol was heated over CaO for 3 hrs, distilled and heated with 60 g Na until 2/3 of the metal was consumed. Thereafter a second 60 g portion of Na was added and the alcohol distilled. Solvents were removed *in vacuo* on rotatory evaporator at a bath temperature not exceeding 30°. Mps (uncorrected) were determined on a Boëtius apparatus. Specific rotations were taken on a Zeiss polarimeter. The homogeneity of the products was checked on silica gel plates (DC Alufolien Kieselgel Merck No. 5553) in the following solvent systems: A = chloroform-methanol-acetic acid (95:5:3), B = chloroform-methanol-concd ammonia (6:5:1), C = chloroform-pyridine (20:1), D = benzene-pyridine-acetic acid (20:2:1), E = isopropanol-water (7:3). Spots were visualized with chlorine-tolidine reagent.

α-*t*-Butyl-γ-Methyl-N-Carbobenzoxy-L-Glutamate.- A stirred solution of Z-Zlu(OMe)[8] (127.1 g, 0.516 mol) in dried *t*-BuOH (1.00 L) and dried pyridine[9] (0.45 L) was cooled to -5° and $POCl_3$ (47.3 mL), 0.516 mol) dropped over 30 min while the temperature was maintained at -5°. The reaction mixture was stirred for 15 min at -5° and then for 40 min at 20°. Evaporation of the solvent left a residue which was dissolved in water (300 mL). The resulting aqueous solution was extracted with ether (2 x 300 mL) and the ethereal extract was washed with a saturated $NaHCO_3$ solution (2 x 300 mL), brine (2 x 300 mL) and dried over Na_2SO_4. Evaporation of the solvent left 136.7 g (90%) of a colorless oil, R_f: A - 0.77, C - 0.61, D - 0.58, E -

0.80.

Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 4.00

Found: C, 61.11; H, 7.25; N, 4.40

α-t-Butyl-N-Carbobenzoxy-L-Glutamate.- Z-Glu(OMe)-OtBu was hydrolyzed according to the procedure of Camble[2] to give a 68% yield of product, mp. 82-83.5°, $[\alpha]_D^{20}$ = -26.6° (c 1.2 MeOH), lit.[2] mp. 82-84°, $[\alpha]_D^{20}$ = -26.6° (c 1.2 MeOH), lit.[10] mp. 82-83.5°, $[\alpha]_D^{25}$ = -27.3° (c 3 MeOH). R_f: A - 0.46, B - 0.69, D - 0.43, E - 0.68.

Anal. Calcd for $C_{17}N_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15

Found: C, 60.48; H, 6.83; N, 4.28

α-Benzyl-N-t-Butyloxycarbonyl-L-Glutamate.- To a stirred solution of Boc-Glu (98.9 g, 0.4 mol) in DMF (100 mL) of constant temperature (25°), was added dropwise triethylamine (55.5 mL, 0.4 mol) over 15 min and then benzyl bromide (52.3 mL. 0.44 mol) over 7 min. Stirring was continued for 10 hrs at room temperature. Water (800 mL) was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate (3 x 400 mL). The organic layer (A) was extracted with 1N Na_2CO_3 (400 mL and 2 x 100 mL) and the aqueous extract then acidified with 1.3N HCl to pH 2 and extracted with ethyl acetate (300 mL and 2 x 200 mL). The organic layer (B) was washed with 0.02N K_2CO_3 solution (7 x 500 mL), 0.02N K_2CO_3 saturated with NaCl (500 mL) and brine (2 x 100 mL). After drying over Na_2SO_4, the solvent was evaporated and the residue crystallized from ethanol to give 59.4 g (44%) of product, mp. 93-93.5°, $[\alpha]_D^{25}$ = -30.3° (c 1 MeOH), lit.[4] mp. 93-93.5°, $[\alpha]_D^{25}$ = -30.2° (c 1 MeOH), lit.[7] mp. 94-95°, $[\alpha]_D^{22}$ = -30.5° (c 1 MeOH). R_f: A - 0.50, B - 0.64, D - 0.58, E - 0.80.

Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15

Found: C, 60.59; H, 6.93; N, 4.08

REFERENCES

1. E. Taschner, C. Wasilewski, T. Sokolowska and J. F. Biernat, Ann., 646, 127 (1961).

2. R. Camble, R. Purkayastha and G. T. Young, J. Chem. Soc. C, 1219 (1968).

3. E. Taschenr, J. F. Biernat, B. Rzeszotarska and C. Wasilewski, Ann., 646, 123 (1961).

4. E. Schröder and E. Kliegier, ibid., 673, 196 (1964).

5. P. G. Pietta and M. Cavallo, J. Org. Chem., 36, 3966 (1971).

6. G. H. L. Nefkens and R. J. F. Nivard, Rec. Trav. Chim. Pays-Bas, 83, 199 (1964).

7. J. Halstrom, O. Schou, K. Kovacs and K. Brunfeldt, Z. Physiol. Chem., 351, 1576 (1970); CA., 74, 88276f (1971).

8. R. A. Boissonnas, S. Guttmann, P. A. Jaquenoud and J. P. Walter, Helv. Chim. Acta, 38, 1491 (1955).

9. "Organicum. Organisch-Chemisches Grundpraktikum", 15. Auflage VEB Deutscher Verlag der Wissenschaften, Berlin 1981, p. 802.

10. M. Hollosi, M. Kajtar and V. Bruckner, Acta Chim. Acad. Sci. Hung., 62, 305 (1969), CA., 72, 44109h (1970).

SYNTHESIS OF 8-HYDROXY-1-NAPHTHALDEHYDE

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As part of our studies on insect growth inhibition and feeding deterrency involving gossypol and related terpene aldehydes, it was of interest to investigate the least complicated example, 8-hydroxy-1-