A Novel Method for the Preparation of *p*-Methoxybenzyloxycarbonyl Amino Acids

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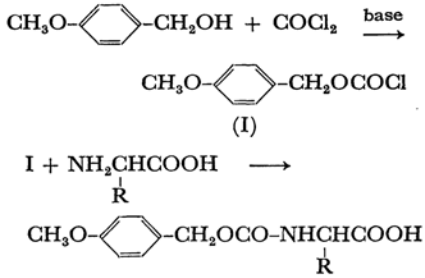
The *p*-methoxybenzyloxycarbonyl (*p*MZ-) group[1,2] has been widely used as a blocking substituent of the amino moiety of amino acids in peptide synthesis. In the present investigation, it was found that *p*MZ-amino acids were prepared directly from a number of amino acids and *p*-methoxybenzyl chloroformate[3,4] (I) under the conditions of the Schotten-Baumann reaction. The reagent (I) was prepared as follows: a solution of anisyl alcohol (12.4 m*l*, 0.1 mol) in dry ether (100 m*l*) was added to a solution of phosgene (21 m*l*, 0.3 mol) in dry ether (100 m*l*) over a period of 10 min. Then a solution of dimethylaniline (12.7 m*l*, 0.1 mol) in dry ether (100 m*l*) was added dropwise over a period of 1 hr, and the mixture was stirred for 2 hr at −5—−10°C. After filtration of the salt formed in the reaction, the filtrate was evaporated under reduced pressure to an oily residue at below 0°C. Twice more dry ether (100 m*l*) was added and evaporation was repeated to remove excess phosgene. This residue was immediately dissolved in tetrahydrofuran (70 m*l*) and the solution was ready for the next reaction.

The solution of the chloroformate was added little by little over a period of 10 min to a solution of



0.05 mol of the amino acid in 200 m*l* of *N* sodium hydroxide (L-glutamic acid: 1.5 N sodium hydroxide) containing tetrahydorfuran (40 m*l*) with vigorous stirring at 0—5°C. This stirring was continued for 2 hr; then the reaction mixture was washed with ether (100 m*l*) and acidified by the addition of solid citric acid. The product was extracted with ethyl acetate (500 m*l*). This layer was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to a residue, which was then crystallized from ethyl acetate-petroleum ether. If the product did not crystallize at this stage, the residue was neutralized with a calculated amount of dicyclohexylamine in ether, and the *p*MZ-amino acid was crystallized as the dicyclohexylammonium salt.

By the present method the following compounds were obtained:

*p*MZ-glycine (80.0%), mp 95—98°C*1 (lit.,[3] mp 95—98°C).

*p*MZ-L-alanine (65.4%), mp 78—81°C,*1 $[\alpha]_D^{22}$ −11.5 (*c* 2.0, acetic acid) [lit.,[2] mp 74—75°C, $[\alpha]_D^{22}$ −11.9 (*c* 3.11, acetic acid)]. (Found: C, 56.94; H, 5.83; N, 5.70%. Calcd for $C_{21}H_{15}NO_5$: C, 56.90; H, 5.98; N, 5.54%.)

*p*MZ-L-glutamic acid (46.1%), mp 109—112°C,*1 $[\alpha]_D^{22}$ −5.6 (*c* 2.0, acetic acid) [lit.,[2] mp 109—111°C, $[\alpha]_D^{22}$ −7.44 (*c* 2.02, acetic acid)]. (Found: C, 53.76; H, 5.22; N, 4.58%. Calcd for $C_{14}H_{17}NO_7$: C, 54.00; H, 5.50; N, 4.50%.)

*p*MZ-L-leucine dicyclohexylammonium salt (88.7%), mp 159—162°C,*1 $[\alpha]_D^{21}$ −6.0 (*c* 2.0, methanol) [lit.,[2] mp 162°C, $[\alpha]_D^{24}$ −6.67 (*c* 2.1, methanol)]. (Found: C, 68.04; H, 9.07; N, 6.01%. Calcd for $C_{27}H_{44}N_2O_5$: C, 68.03; H, 9.31; N, 5.88%.)

α-*N*-*p*MZ-*δ*-*N*-Cbz*2-L-ornithine dicyclohexylammonium salt (33.4%), mp 133—135°C,*1 $[\alpha]_D^{19}$ +6.3 (*c* 2.0, methanol). (Found: C, 66.91; H, 7.91; N, 6.94%. Calcd for $C_{34}H_{49}N_3O_7$: C, 66.75; H, 8.07; N, 6.87%.)

A full report will be presented in a subsequent paper.

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*1 All melting points are uncorrected.

*2 Cbz: benzyloxycarbonyl.