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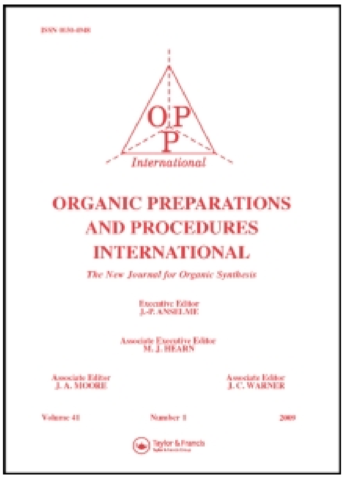

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SYNTHESIS OF *t*-BUTOXYCARBONYL AND BENZYLOXYCARBONYL AMINO ACID AMIDES

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product collected, washed with water, dried and crystallized. The reaction mixture may also be evaporated to dryness and treated with water and ether as described above.

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SYNTHESIS OF t-BUTOXYCARBONYL AND BENZYLOXYCARBONYL AMINO ACID AMIDES

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A series of amides of Boc-[1] and Z-amino acid (Table) was needed in amounts ≥100 mmoles for α,β-dehydropeptide synthesis.[2] We have found the amides to be easily obtained directly from Boc- and Z-amino acid by means of isobutyl chlorocarbonate and of a large excess on concentrated aqueous ammonia, thus alleviating the need to use active esters and organic solvents saturated with gaseous ammonia. Our procedure is economical for scale-up preparation of amides and is comparable (yields, specific rotations and mps.) to a frequently used p-nitrophenyl ester ammonolysis.[3-5] Ammonolysis of mixed anhydrides in anhydrous media has not led to superior yield (Table; values in parenthesis) as reported.[6]

EXPERIMENTAL SECTION

If solvents had to be evaporated, a rotary evaporator (vacuum) and a bath of temperature not exceeding 30° were used. $KHCO_3$ denotes a 50:50 mixture of saturated $KHCO_3$ and saturated NaCl. 2 N HCl denotes solution saturated with NaCl. Crystallization solvents, yields, melting points (uncorrected, Boetius apparatus), specific rotations (Zeiss polarimeter Palamat A) and R_f coefficients of the obtained Boc- and Z-amino acid amides are listed in Table. All of the amides were identified by elemental analysis and their homogeneity was checked on silica gel plates (DC Alufolien Kieselgel Merck 5553) at least in one of each of the acidic, basic, amphoteric and neutral solvent systems. R_f values given in the Table refer to solvent systems diagnostic for all the compounds: A = chloroform-methanol-acetic acid (95:5:3), B = benzene-methanol-acetone-pyridine (6:2:1:1), C, = benzene-methanol-acetone-pyridine-acetic acid (12:2:1:1:0.5), D = chloroform-methanol-acetone (1:0.75:1). Spots were visualized with chlorine-tolidine reagent.

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Boc- and Z-Amino Acid Amides.- To a stirred solution of Boc- or Z-Amino acid (0.2 mol) in THF (200 ml) cooled to -45°, N-methylmorpholine (22.2 ml, 0.2 mol) and isobutyl chlorocarbonate (26.3 ml, 0.2 mol) were added. After 10 min. the reaction mixture was cooled to -55°, and conc. aqueous ammonia (50 ml, 0.7 mol) was added; the reaction mixture was cooled again to -55° and the same amount of the conc. ammonia was added again. The mixture was stirred for 5 hrs at -15°. The workup depended on individual amide solubility.

$Boc-Gly-NH_2$.- The solvent was evaporated, EtOAc (800 ml) was added and N-methylmorpholine hydrochloride filtered. The filtrate washed with $KHCO_3$ (100 ml) and 2N HCl (100 ml) and the organic phase dried with anhydrous Na_2SO_4. The solvent evaporated and the residue crystallized. For Boc-Phe-

TABLE. Boc- and Z-Amino Acid Amide

Amide of	Yield[e] (%)	mp.[f] (°)	R_f Coefficients A	B	C	D	[α]D (°)	lit. [α]D (°)
Boc-Gly[a]	83 (90)	98-99.5 (95)[7]	0.47	0.51	0.45	0.70		
Boc-Phe[b]	93	149.5-152 (--)[8]	0.72	0.71	0.51	0.80	+13.2[g] (c 1.60)	
Boc-Val[b]	95 (87)	160.5-162 (156-157)[9]	0.52	0.75	0.67	0.73	+10.7[h] (c 1.00)	
Z-Gly[c]	86 (83)	139-141 (138-139)[4]	0.40	0.62	0.25	0.76		
Z-Phe[b]	94	165-167 (167)[10]	0.75	0.71	0.48	0.80	-17.7[i] (c 2.00) +13.5[g] (c 1.00)	-6.3[i,5] (c 2.00) +12.0[g,10] (c 1.00)
Z-Val[d]	98	211-212.5 (212)[3]	0.73	0.78	0.45	0.42	+25.6[i] (c 1.03)	+22.6[i,3] (c 1.00)

a) From EtOAc-pet ether. b) From MeOH-H_2O. c) From $CHCl_3$. d) From MeOH. e) Yield with isobutyl chlorocarbonate in anhydrous organic solvents in parenthesis. f) Highest mp. reported in parenthesis. g) In $CHCl_3$. h) In EtOAc. i) In DMF.

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NH_2, Boc-Val-NH_2, Z-Gly-NH_2 and Z-Phe-NH_2, brine (400 ml) was added to the reaction mixture and in the case of Z-Phe-NH_2 as much THF as necessary was poured to dissolve the amide precipitate. The organic phase was separated and washed with $KHCO_3$ (40 ml) and 2N HCl (2 x 40 ml) and the THF evaporated. The residue was dissolved in the appropriate solvent (if necessary the NaCl was filtered) and crystallized. For Z-Val-NH_2, brine (400 ml) was added to the reaction mixture and the amide was collected and crystallized.

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Found: C, 63.50; H, 7.78; N, 10.48.
PMR (Tesla spectrometer 100 MHz BS 487; in DMSO in HMDS presence, at 22°) δ: 1.5 (s, 9, Boc), 3.1 (m, 2, CH_2Ph), 4.3 (m, 1, αCH), 7.4 (m, 5, ArH); IR (Zeiss spectrometer Specord 71 at KBr pellets): 3380 m, 3300 m (N-H), 3100w, 2880w (C-H), 1680s (I amide), 1510s (II amide), 1495m, 1040m, 1015m (Ar).

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