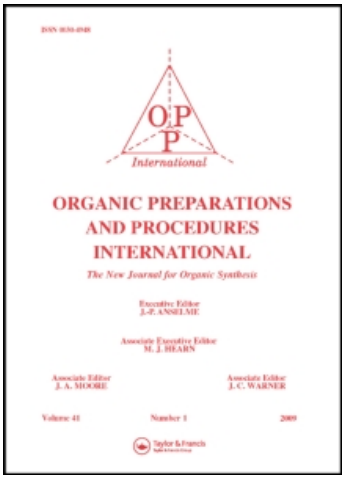

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A ONE-POT SYNTHESIS OF N^{α}BENZYLOXYCARBONYL N^{ω}-*t*-BUTOXYCARBONYL-L-ORNITHINE AND L-LYSINE

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2H, CH_2), 3.88 (m, 1H, H-1 of cyclohexyl), 2.32 (s, 3H, $CH_2C_6H_4CH_3$), 2.27 (s, 3H, $C_6H_4CH_3$).
Anal. Calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.27; N, 7.21. Found: C, 77.48; H, 7.20; N, 7.12
5k: mp. 155-156°; 53% yield; IR: 3314, 1631 cm^{-1}; ^1H NMR: δ 6.23 (d, 1H, NH, J = 7.9 Hz), 4.10 (m, 1H, H-1 of cyclohexyl), 2.53 (s, 3H, CH_3).
Anal. Calcd. for $C_{18}H_{21}ClN_2O_2$: C, 64.96; H, 6.36; N, 8.42. Found: C, 64.83; H, 6.48; N, 8.46
5l: mp. 142-143°; 54% yield; IR: 3325, 1632 cm^{-1}; ^1H NMR: δ 6.18 (d, 1H, NH, J = 7.9 Hz), 4.18 (s, 2H, CH_2), 4.04 (m, 1H, H-1 of cyclohexyl).
Anal. Calcd for $C_{24}H_{25}ClN_2O_2$: C, 70.50; H, 6.16; N, 6.85. Found: C, 70.41; H, 6.29; N, 6.99

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A ONE-POT SYNTHESIS OF N^{α}-BENZYLOXYCARBONYL-N^{ω}-*t*-BUTOXYCARBONYL-L-ORNITHINE AND L-LYSINE

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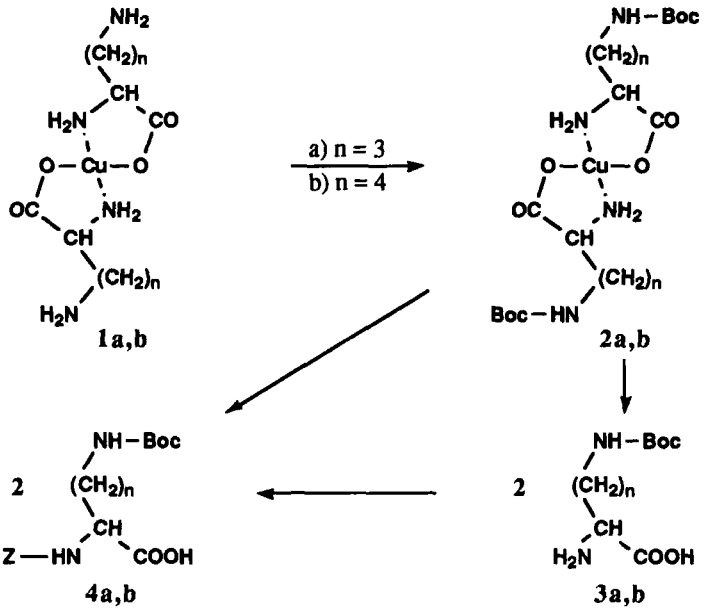
The title compounds Z-Orn(Boc)[1] and Z-Lys(Boc) serve as valuable intermediates in Schwyzer's strategy of peptide chain assembly using the benzyloxycarbonyl group for temporary protection of α-amino functions and the *t*-butyl type group for permanent protection of side-chain

functions.[2,3] With the exception of one special approach,[4] these derivatives are currently obtained *via*



the simple copper complex (**1**) which is ω-*t*-butoxycarbonylated (**2**), followed by removal of copper in a separate step (**3**) and finally the α-amino group is benzyloxycarbonylated. The earlier syntheses of these materials, according to this scheme suffer from several drawbacks.[4] The main problem was the low yield of isolated **3** due to the solubility of these compounds in aqueous media. Therefore, an improved procedure has been proposed in which copper is removed from **2** with a chelating ion exchange resin. However, the handling and regeneration of this resin is rather troublesome.[4] Herein we report on a simple synthesis of Z-Orn(Boc) and Z-Lys(Boc). The previous separate removal of copper is omitted and the α-benzyloxycarbonylation being carried out directly on the ω-*t*-butoxycarbonylated copper complex (**2**) in the presence of EDTA. In this manner, the burdensome usage of the chelating ion exchange resin has been eliminated.

For the copper complex formation, we employed readily available $CuSO_4 \cdot 5H_2O$ instead of the most frequently used $CuCO_3 \cdot Cu(OH)_2 \cdot H_2O$. Applied ornithine obtained from Reanal, contained largely tolidine-positive, ninhydrin-negative contaminants. Since the ornithine copper complex does not dissolve in methanol, those impurities could be easily removed by filtration. For the α-benzyloxycarbonylation, benzyl 8-quinolylformate was used.[5] Benzyl chloroformate gave a more complex crude reaction mixture and the yield was somewhat lower; however, it may be used instead of the 8-quinolylformate. Z-Lys(Boc) was isolated as the dicyclohexylammonium (DCHA) salt.[6] The procedures described afford final products **4a** and **4b•DCHA** in high yields and of high purity.

EXPERIMENTAL SECTION

Purified solvents (Polskie Odczynniki Chemiczne) were stored over drying agents. Organic solutions

were dried with anhydrous Na_2SO_4. Solvents were removed from reaction mixtures *in vacuo* on a rotatory evaporator at a bath temperature not exceeding 30°C. Reactions were monitored and the homogeneity of intermediates and final products was checked on silica gel plates (DC Alufolien Kieselgel 60 No 5553 Merck) in the following solvent systems: A = benzene-methanol-acetone-pyridine-acetic acid (24:4:2:2:1), B = chloroform-methanol-acetic acid (95:5:3), C = benzene-methanol (4:1), D = chloroform-methanol-dioxane-conc. ammonia (12:7:5:1). Spots were visualized with ninhydrin and chlorine-KI-tolidine reagent. Mps. were determined on a BOËTIUS heating block and are given uncorrected. HPLC analyses were carried out using "System Gold" for Methods Development consisting of a Model 126 programmable solvent module, a Model 168 diode array detector, operating at λ = 210 nm, a Model 210A injector valve (all from Beckman) and PC 386SX (Wearnes) with "System Gold" version 5.1 software for data collection and controller function. A column 120 x 4 mm with a precolumn 5 x 4 mm, Hypersil ODS 3 µm and 0.1% trifluoroacetic acid-acetonitrile (60:40) as a mobile phase were applied. The flow rate was 1 mL/min.

N^{α}-Benzyloxycarbonyl-N^{δ}-*t*-butoxycarbonyl-L-ornithine (4a).- To a stirred solution of HCl•Orn (Reanal) (9.8848 g, 58.6 mmol) in 1N NaOH (58.6 mL), $CuSO_4 \cdot 5H_2O$ (7.3159 g, 29.3 mmol) in water (32 mL) was added. After 1.5 hrs, water was evaporated, methanol added, a precipitate filtered off and washed with dioxane and methanol. To the precipitate (**1a**) 1N $NaHCO_3$ (110 mL) and *t*-butyl pyrocarbonate (18.6604 g, 82.5 mmol) in dioxane (110 mL) were added. Stirring was continued for 3 days, CO_2 removed and the precipitate was collected and washed with water and diethyl ether to give **2a** (13.7738 g; 79% yield). To **2a** (12.7191 g, 24.2 mmol) 1N NaOH (121 mL), EDTA (13.51 g, 36.3 mmol) and water (100 mL) were added. Stirring was continued for 2.5 hrs and water was concentrated to about half its volume and a solution of benzyl 8-quinolylcarbonate[5] (20.2772 g, 72.6 mmol) in dimethylformamide (110 mL) introduced. The mixture was left stirring overnight. The solvents were evaporated, the residue dissolved in water (250 mL) and extracted with ethyl acetate. The aqueous layer was acidified with 2N HCl to pH 3 and extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated and the residue crystallized from ethyl acetate-petroleum ether to furnish **4a** (14.5517 g; 82% yield), homogeneous by TLC, mp. 99.5-101°, lit.[7] mp. 97-99°, lit.[8] mp. 71°. R_f: A - 0.58, B - 0.40, C - 0.23, D - 0.45. HPLC: tR = 4.71 min; 99.75% purity.

N^{α}-Benzyloxycarbonyl-N^{ϵ}-*t*-butoxycarbonyl-L-lysine (4b).- To a stirred solution of HCl•Lys (Reanal) (9.1325 g, 50 mmol) in 1N NaOH (50 mL) $CuSO_4 \cdot 5H_2O$ (6.245 g, 25 mmol) was added. After 1.5 hr, 1N $NaHCO_3$ (100 mL) and a solution of *t*-butyl pyrocarbonate (16.37 g, 75 mmol) in dioxane (110 mL) were added. Stirring was continued for 20 hrs, CO_2 removed and the precipitate was collected and washed with water and diethyl ether to afford **2b** (12.5531 g; 91% yield). The combined amount of **2b** was α-benzyloxycarbonylated and worked up as described for **2a**. The crude product was dissolved in ethyl acetate (80 mL), treated with dicyclohexylamine (10.44 mL; 52.2 mmol) and left standing overnight. The precipitate was collected, washed with ethyl acetate and diethyl ether to furnish **4b•DCHA** (23.12 g; 91% yield) homogeneous by TLC, mp. 154-155.5°, lit.[4] mp. 154.5-155°. R_f: A - 0.61, B - 0.46, C - 0.26, D - 0.47. HPLC: tR = 5.93 min; 98.95% purity.

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1. Abbreviations used: Boc = *t*-butoxycarbonyl, z = benzyloxycarbonyl, Lys = lysine, Orn = ornithine, EDTA = ethylenediamine tetraacetic acid.

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SYNTHESIS OF DIFLUORODURENE AND DIFLUOROPYROMELLITIC ACID

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Practical molar scale syntheses of the commercially unavailable dichloro- and dibromopyromellitic acid by a two-step oxidation of the corresponding dihalodurenes have been developed earlier in this laboratory.[1] Our interest in the preparation of hitherto unknown difluoropyromellitic acid (**8**), required significant quantities of difluorodurene (**7**). Stavber and Zupan[2] had reported the isolation of small amounts (30 mg, 9% yield) of compound **7** from a mixture of products obtained by fluorination of durene with xenon difluoride. We now describe a six-step synthesis of difluorodurene (**7**) from readily accessible dinitrodurene (**1**)[3] and the oxidation of **7** to difluoropyromellitic acid (**8**).

Dinitrodurene (**1**) was reduced with sodium disulfide to *p*-aminonitrodurene,[4,5] isolated as its