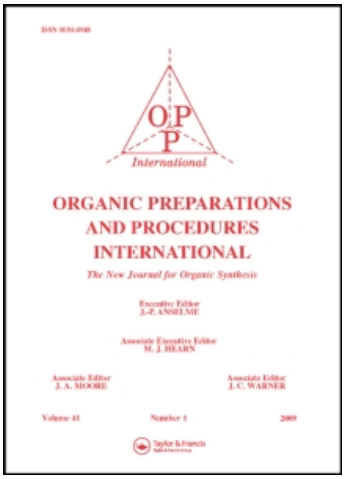

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AN IMPROVED PREPARATION OF N-BENZYLOXYCARBONYL-L-LYSINE METHYL ESTER HYDROCHLORIDE

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AN IMPROVED PREPARATION OF N-BENZYLOXYCARBONYL-L-LYSINE METHYL ESTER HYDROCHLORIDE

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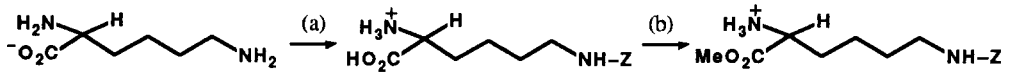
The difficulties encountered in obtaining N-Cbz-Lys-OMe•HCl prompted us to reexamine the known procedures to prepare the title compound. Therefore, we modified the method of Eckstein et al.[1] Since the EDTA-Cu^{2+} complex cannot form or is very unstable in acidic medium, the N-Cbz-Lys-OH from N-Cbz-Lys-Cu^{2+} was liberated with EDTA in the presence of a minimum amount of HCl used to maintain the pH at 7.0, in this way, the N-protected amino acid was obtained in good



a) Cu+; $PhCH_2OCOCl$; EDTA: H^+ b) $SOCl_2$, -10°, MeOH

yields. In order to prepare the methyl ester hydrochloride of N-Cbz-Lys-OH, the thionyl chloride method[2] was used instead of boron trifluoride-methanol esterification suggested by Coggis et al.[3] However, the simple and efficient extraction procedure of the latter authors was retained; the yield of this step was over 90%.

EXPERIMENTAL SECTION

N-Benzyloxycarbonyl-L-lysine.- To solution of L-Lys•HCl (18.25 g, 100 mmol) and NaOH (8 g, 200 mmol) in water (80 ml) was added a solution of cupric sulfate pentahydrate (12.5 g, 50 mmol) in water (40 ml) at 30°. After cooling to 0°, sodium bicarbonate (10 g, 120 mmol) was added followed by the dropwise addition of benzyl chloroformate (19 ml, 130 mmol). The reaction mixture was stirred at 0° for 3 hrs and then at room temperature overnight. The N-Cbz-Lys-Cu^{2+}-complex precipitate was collected and washed with water (200 ml) and acetone (100 ml) then dried. To a boiling suspension of EDTA (40 g, 110 mmol) in water (400 ml), the powdered N-Cbz-Lys-Cu^{2+} complex was added portionwise, while the pH was maintained at 7.0 by addition of conc. HCl (10 ml). The white precipitate was collected, washed with water and methanol and dried. The product was recrystallized from ethanol-water to afford the desired compound (22 g, 80%), mp. 252-254°, $[\alpha]_D^{25} = +13.7°$, (c = 1.80, 6M HCl), lit.[1] mp. 254° and $[\alpha]_D^{27} = +13.8°$, (c = 1.66, 6 M HCl).

Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.91; H, 7.13; N, 9.98. Found: C, 59.60; H, 7.14; N, 9.94

N-Benzyloxycarbonyl-L-lysine Methyl Ester•HCl.- A solution of N-Cbz-Lys-OH (10 g, 36.0 mmol) in dry methanol (50 ml) was added dropwise to thionyl chloride (2.60 ml, 36.0 mmol) at -10°. The reaction mixture was stirred at -15° for 1 hr and then at room temperature for 30 hrs. The solvent was removed under reduced pressure and the crude product co-evaporated with methanol (3 x 50 ml). The oily residue was dissolved in water (50 ml) and the pH was adjusted to 9.0 by the addition of 5M NaOH. After saturation of the solution with sodium chloride, ethyl acetate (100 ml) was added and the suspension was filtered to remove unreacted N-Cbz-Lys-OH. The organic layer was separated from the filtrate and the aqueous layer was extracted twice with ethyl acetate (2 x 50 ml). The combined organic phase was dried and the solvent was removed under reduced pressure. The residue was diluted with methanol (20 ml), then with 5 ml of methanol saturated with HCl gas. The mixture was cooled in an ice-bath. Ether (250 ml) was then added slowly and the N-Cbz-Lys-OMe•HCl, which precipitated as white crystals, was collected (11 g, 93%), mp. 117-118°, $[\alpha]_D^{25}$ = 15.0°, (c = 0.66, MeOH), lit.[3] mp. 117-118°, $[\alpha]_D^{27}$ = 15.5°, (c = 2.0, H_2O).

^1H NMR (DMSO-d_6): δ 1.12-1.62 (m, 4 H, $2CH_2$), 1.7 (m, 2 H, CH_2), 2.97 (m, 2 H, CH_2), 3.40 (s, 1 H, NH), 3.75 (s, 3 H, OCH_3), 3.95 (m, 1 H, CH), 5.00 (s, 2 H, OCH_2), 7.36 (s, 5 H, C_6H_5), 8.75 (s, 2 H, NH_2).

Anal. Calcd for $C_{15}H_{22}N_2O_4$•HCl: C, 54.41; H, 6.95; N, 8.46
Found: C, 54.24; H, 6.94; N, 8.44

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