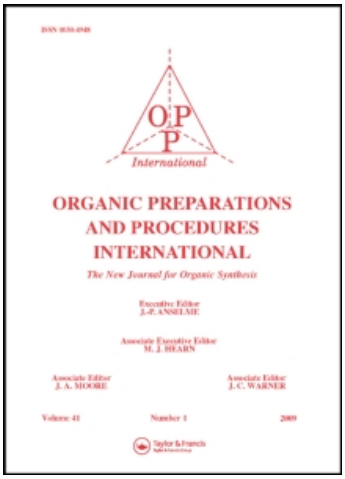

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AN IMPROVED SYNTHESIS OF N^{ε}-FMOC-L-LYSINE AND N^{δ}-FMOC-L-ORNITHINE

Maria Henczi[a]; Donald F. Weaver[b]
[a] Departments of Chemistry, Medicine Queen's University, Kingston, Ontario, Canada [b] Medicine Queen's University, Kingston, Ontario, Canada

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AN IMPROVED SYNTHESIS OF N^{ε}-FMOC-L-LYSINE AND N^{δ}-FMOC-L-ORNITHINE

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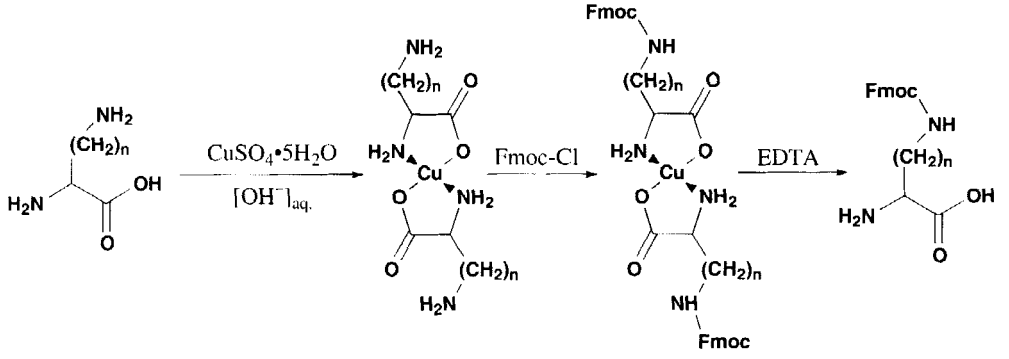
Maria Henczi[†] and Donald F. Weaver*[††]

Departments of Chemistry[†] and Medicine[††]
Queen's University, Kingston, Ontario, CANADA, K7L 3N6

The selective introduction of a readily removed amine protecting group into the side-chain of a dibasic amino acid permits the synthetically desirable objective of side-chain modification to a "non-natural/atypical" residue following the synthesis of the backbone. The 9-fluorenylmethoxycarbonyl (Fmoc) group, which is easily deblocked under mild basic conditions[1] and is compatible with either *t*-



butoxycarbonyl (Boc)[2] or carbobenzoxy (Cbz)[3] N^{α} protection, is an ideal candidate for selective side-chain amine protection. This communication reports the specific introduction of the Fmoc functionality into the side-chain amino group of dibasic amino acids using copper salts[4] to complex the α-amino and carboxyl groups and thus block the reaction of the α-amino group.

The copper (II) complexes (**2**) were synthesized by reacting the fully unprotected amino acid (**1**) with $CuSO_4 \cdot 5H_2O$ in an alkaline aqueous solution. The resulting amino acid copper (II) complex underwent selective side-chain protection by subsequent dropwise addition of 9-fluorenylmethyl chloroformate (Fmoc-chloride) (**3**). The modified complex was then decomposed to afford the Fmoc-protected product **4** using ethylenediaminetetraacetic acid (EDTA)[5] as the complexing agent. This method was successfully applied to the syntheses of N^{ε}-Fmoc-L-lysine and N^{δ}-Fmoc-L-ornithine. A synthesis of N^{ε}-Fmoc-L-lysine reported by Albericio and his group[6] gave a 64% yield of **3** using Fmoc-azide as the protecting group reagent which helps to reduce the formation of Fmoc-dipeptides[7] as undesired synthetic by-products. The route employed here uses the less hazardous and more easily handled Fmoc-chloride, and avoids the formation of dipeptides through the use of a copper salt to simultaneously inactivate the α-amino and carboxyl groups.

EXPERIMENTAL SECTION

Capillary melting points were recorded on a MEL-TEMP-II apparatus and are reported uncorrected. Infrared spectra were determined on a BOMEM MB-120 model, and $^{1}H/^{13}C$ NMR spectra on a Bruker AC-400 spectrometer. Elemental analyses were carried out by Guelph Chemical Laboratories. Mass spectra data were obtained on a Fisons VG Quattro instrument by the fast atom bombardment technique. All the starting reagents were purchased from Aldrich; solvents were obtained from BDH.

Preparation of N^{ε}-Fmoc-L-Lysine Copper Complex.- L-Lysine monohydrochloride (1.1g, 6.0mmol) was dissolved in water (10mL) containing sodium hydroxide (0.2g, 6.0mmol). Cupric sulfate pentahydrate (0.8g, 3.2mmol) in water (10mL) was mixed with the above solution. To the resulting deep blue solution stirred and cooled in an ice bath, was added sodium bicarbonate (0.6g, 7.0mmol) in one sum and a solution of 9-fluorenylmethyl chloroformate (1.6g, 6.2mmol) in 5 mL of dioxane was introduced dropwise over 5 minutes. The reaction mixture was stirred overnight at room temperature. The resultant blue precipitate was collected and washed with cold water (10mL), ethanol (10mL) and ethyl acetate (10mL) to yield 4.1g (85%) of blue solid, lit.[6] yield: 64%, mp. 211-213°, lit.[6] mp. 212-213°; IR (KBr): 3320, 3280, 2933, 2870, 1693, 1621, 1532, 1448, 1254, 1133, 758, 773. FAB-MS:(m/z) 798.94, 369.02.

Preparation of N^{ε}-Fmoc-L-Lysine.- To a solution of the finely powdered copper (II) complex (1.0g, 1.3mmol) in water (60mL), was added EDTA (0.6g, 1.6mmol). The solution was stirred for 2 hrs at 80°. The white crystalline final product was collected and washed with cold water (20mL), and ethanol (20mL) to yield 0.5g (99%), lit.[6] yield: 96%; mp. 210-212°, lit.[6] mp. 209-211°. ^{1}H NMR (DMSO-d_6): δ 1.3-1.9 (m, 6H, H-3, H-4, H-5), 2.6-2.7 (q, 2H, H-6), 3.1-3.2 (q, H-2), 3.5-3.7 (m, C<u>H</u>Fm), 6.2 (m, 2H, C<u>H</u>$_2$Fm), 7.3-7.4 (m, 4H$_{arom}$), 7.8-7.9 (m, 4H$_{arom}$).

^{13}C NMR (DMSO-d_6 at 333K): δ 25.33 (C-4), 31.34 (C-3), 38.78 (C-5), 43.27 (C-6), 45.72 (C-2), 53.16 (<u>C</u>H-Fm), 108.97 (<u>C</u>H$_2$Fm), 119.59, 120.96, 126.90, 128.55 (<u>C</u>H$_{arom}$, Fm), 137.19, 139.18 (C$_{arom}$, Fm), 142.41 (C-1), 155.99 (COFm). FAB-MS: (m/z) 369.02 [M+1].

IR (KBr): 3372, 3000, 3910, 1697, 1610, 1590, 1550, 1450, 1393, 1349, 1253, 1147, 1003, 758, 737.

Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.56; N, 7.60. Found: C, 68.57; H, 6.75; N, 7.68

The procedure for the selective protection of L-ornithine was the same as described above.

N^{δ}-Fmoc-L-ornithine Cu-complex: Yield: 91%, mp. 207-209°; IR (KBr): 3310, 3280, 3000, 2850, 1690, 1616, 1534, 1447, 1393, 1258, 1132, 757, 736. FAB-MS: (m/z) 770.00, 355.05.

N^{δ}-Fmoc-L-ornithine: Yield: 92%, mp. 152-154°; ^{1}H NMR (DMSO-d_6): δ 1.4-2.1 (m, 4H, H-3, H-4), 2.6 (q, H-2), 3.0-3.1 (q, 2H, H-5), 3.3-3.4 (m, C<u>H</u>Fm), 6.2 (m, 2H, C<u>H</u>$_2$Fm), 7.3-7.4 (m, 4H$_{arom}$), 7.8-7.9 (m, 4H$_{arom}$). ^{13}C NMR (DMSO-d_6 at 333K): δ 24.16 (C-4), 30.65 (C-3), 43.72 (C-2), 46.26 (C-5), 53.15 (<u>C</u>H-Fm), 108.97 (<u>C</u>H$_2$Fm), 119.59, 120.96, 126.90, 128.55 (<u>C</u>H$_{arom}$, Fm), 137.19, 139.18 (C$_{arom}$, Fm), 142.41 (C-1), 155.99 (COFm). FAB-MS: (m/z) 355.05 [M+1]. IR (KBr): 3510, 3100, 2941, 1770, 1680, 1710, 1690, 1610, 1488, 1419, 1347, 1307, 1268, 1131, 1093, 761, 739.

Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.82; H, 6.38; N, 7.90

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AN EFFICIENT AND CONVENIENT PROCEDURE FOR ESTER HYDROLYSIS

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J. M. Khurana* and Arti Sehgal

Department of Chemistry
University of Delhi, Delhi-110007, INDIA

Ester hydrolysis, an important transformation is usually catalyzed by acids or bases.[1] Although substrates sensitive to hydrolytic conditions may be cleaved by a number of reagents under neutral conditions,[2] most of these reagents have limited applications and are either costly or not readily available. Both acidic and alkaline hydrolyses are equilibrium reactions; however for preparative purposes ester hydrolyses are almost always performed in basic solution in order to shift the equilibrium. To overcome the problem of a heterogeneous system, micellar catalysis[3] and phase transfer catalysis[4] have recently been employed, though the improvement under these conditions is not significant. Moon *et al.*[5] have reported the use of ultrasound to catalyze two-phase ester saponifications. Therefore, search for a simple method for ester hydrolysis having wider application is still warranted. We now report that the hydrolysis of a variety of esters of aromatic, aliphatic and fatty acids with sodium hydroxide in aqueous dimethylformamide proceeds in nearly qnantitative yields in 15-60 min