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Side Reaction during Deprotection of Tryptophan Derivatives by Catalytic Transfer Hydrogenation in Formic Acid

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On catalytic transfer hydrogenation using formic acid and palladium black, 2,3-dihydrotryptophan derivatives were obtained from tryptophan derivatives. The results showed that care is necessary in the removal of protecting groups in peptides containing tryptophans.

Keywords——catalytic transfer hydrogenation; 2,3-dihydrotryptophan; formic acid; palladium black; protecting group; peptide; reduction; tryptophan

Recently, catalytic transfer hydrogenation (CTH) has attracted much attention[1] in relation to peptide synthesis, because CTH easily removes protecting groups without affecting labile functions. Among CTH agents, formic acid has been shown to be an excellent solvent and facile hydrogen donor in CTH of protected peptides.[2] During studies[3] of the reduction of tryptophan derivatives, we considered that tryptophan residues might be reduced to 2,3-dihydrotryptophan residues under the usual formic acid CTH conditions during the removal of protecting groups.

N-Acetyl-L-tryptophan ethyl ester (**1**) was subjected to formic acid CTH over palladium black and the results are presented in the Table I. Under the conditions used, **1** was reduced

TABLE I. Yields of the 2,3-Dihydro Compounds (**2**)[a] during Catalytic Transfer Hydrogenation of *N*-Acetyl-L-tryptophan Ethyl Ester (**1**)

Run	Reaction time (h)	Yield of **2** (%)		Recovery of **1** (%)
		a	b	
1	0.17	1.5	—	83.5
2	0.5	8.5	1.0	82.7
3	2	19.0	1.8	43.3
4	5	29.6	4.8	37.0

a) All products gave satisfactory IR, ^{1}H-NMR, and mass spectra.

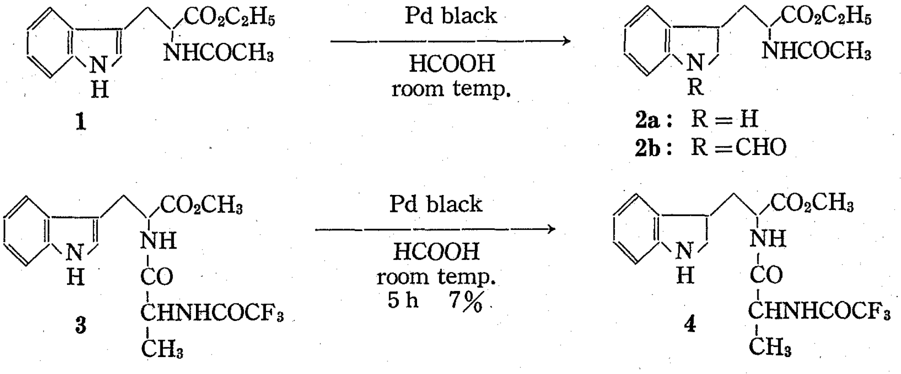

Chart 1

to the 2,3-dihydro compound (2) in unexpectedly high yield (30%) when treated for over 5 hours. However, the benzyloxycarbonyl protecting group is removed rapidly. Z–Ala–Trp–OCH_3 was subjected to formic acid CTH over palladium black and the benzyloxycarbonyl group was removed within 10 minutes without reducing the tryptophyl residue. On the other hand, removal of *N*-benzyl and nitro protecting groups requires 5 hours or more.[2] In such cases, an undesirable side reaction, the reduction of tryptophans, will occur. Next, a dipeptide, TFA–Ala–Trp–OCH_3 (**3**) was subjected to the hydrogenolysis, and TFA–Ala-2,3-dihydro-Trp–OCH_3 (**4**) and **3** were obtained in 7% and 70% yields, respectively. Identification and calculation of yield of **4** were performed by gas chromatographic analysis.

In conclusion, formic acid CTH of protected peptides containing tryptophans will cause the reduction of tryptophan residues to some extent when the reaction time is prolonged. This result means that care is necessary in the removal of protecting groups in peptides containing tryptophans.

Experimental

All melting points are uncorrected. The following instruments were used to obtain physical data: infrared (IR) spectra, Shimadzu IR-400; nuclear magnetic resonance (NMR) spectra (tetramethylsilane as an internal standard), JNM-C-60HL; gas chromatography, Shimadzu GC-4BM; mass spectra (MS), Shimadzu LKB-9000.

Materials——Palladium black and 90% formic acid were purchased from Soekawa Chemical Co. Ltd. and Wako Pure Chemical Industries, Ltd., respectively. Compound **1**, mp 107—108°C (lit.[4] mp 109—109.5 °C) and Z–Ala–Trp–OCH_3, mp 137—138.5°C (lit.[5] mp 138—139°C) were prepared by the reported methods.[4,6] Compound **3**, mp 145—145.5°C, was prepared by a modification of the reported method.[6] *Anal.* Calcd for $C_{17}H_{18}F_3N_3O_4$: C, 52.99; H, 4.69; N, 10.91. Found: C, 53.07; H, 4.79; N, 11.10.

Reduction of 1 to 2a and b——Palladium black (100 mg) was added to **1** (98.6 mg, 0.360 mmol) in 90% formic acid (10 ml) under a nitrogen atmosphere. After 5 h stirring at room temperature, the catalyst was filtered off and washed with 80% aq. MeOH (50 ml). The combined solution was concentrated *in vacuo* at room temperature. The residue was taken up in 10% $NaHCO_3$ and the solution was extracted with AcOEt (30 × 2 ml). The combined extract was washed with sat. NaCl and dried over anhyd. Na_2SO_4. After removal of the solvent by evaporation, the residue was purified by silica gel column chromatography [benzene–acetone (2: 1) for elution] to give **2a** (29.4 mg, yield 29.6%), **2b** (5.2 mg, yield 4.8%), and **1** (36.4 mg, 37.0%). The identity of **2a** was established by comparison of the spectral data with those of the authentic sample.[3] The spectral data for **2b** are as follows: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (CO), 1660 (NCO); NMR ($CDCl_3$) δ: 1.29 (3H, t, $J=7$ Hz), 2.04 (3H, s), 3.01—3.90 (3H, m), 4.20 (2H, q, $J=7$ Hz), 4.49—5.08 (1H, m), 6.96—7.33 (4H, m), 8.50, 8.92 (1H, ss); MS *m/e*: 304 (M^+).

Reduction of 3 to 4——Palladium black (100 mg) was added to **3** (106.7 mg, 0.277 mmol) in 90% formic acid (3 ml) under a nitrogen atmosphere. After 5 h stirring at room temperature, the catalyst was filtered off and washed with 80% aq. MeOH (50 ml). The combined solution was concentrated *in vacuo* at room temperature. The residue was taken up in 10% $NaHCO_3$ and the solution was extracted with AcOEt (30 × 2 ml). The combined extract was washed with sat. NaCl and dried over anhyd. Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography [benzene–acetone (3: 1) for elution] to give a mixture (82.3 mg) of **3** and **4**, which was trifluoroacetylated by the reported method.[7] Identification and calculation of the yield of **4** were performed by gas chromatographic analysis. An authentic sample was obtained by pyridine–borane reduction[3] and subsequent trifluoroacetylation[7] of **3**. Gas chromatographic analysis of the mixture showed the presence of trifluoroacetylated **4** (9%, retention time: 12.1 min) and **3** (91%, retention time: 13.0 min). Gas chromatographic conditions were as follows: glass column (4 m); 10% SE-30 on Chromosorb W (60—80 mesh); temperature, 260°C; carrier gas, N_2 at a flow rate of 50 ml/min.

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