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Cyclisations of Tryptophans. V.† Trifluoroacetylation of N_b-Methoxycarbonyl-L-tryptophan Methyl Ester in Pyridine

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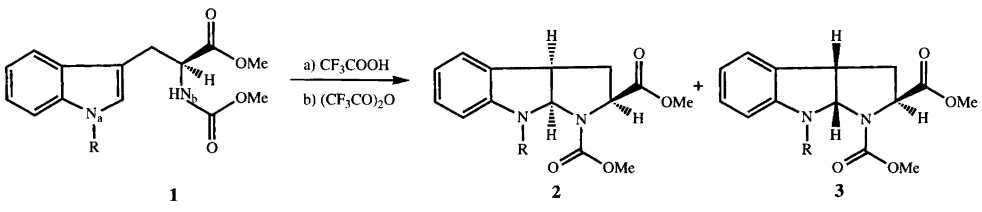
N_b-Methoxycarbonyl-L-tryptophan methyl ester (**1**) reacts with trifluoroacetic anhydride in pyridine to give (2*S*,3a*R*,8a*S*)-3a-(*N*-trifluoroacetyl-1,4-dihydro-4-pyridyl)-1-methoxycarbonyl-2-methoxycarbonyl-8-trifluoroacetyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**4**). In addition N_a-trifluoroacetyl-N_b-methoxycarbonyl-L-tryptophan methyl ester (**1b**) and two diastereomeric (5′*S*)-2,3-dihydro-2-trifluoroacetoxy-1′,5′-bis(methoxycarbonyl)-2′-hydroxy-2′-trifluoromethylspiro[indole-3,3′-pyrrolidine] (**5a**/**5b**) are formed.

Results and discussion

An equilibrated solution of N_b-methoxycarbonyl-L-tryptophan methyl ester (**1a**) in trifluoroacetic acid comprises mainly the tricyclic 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole tautomer **2a** with the *C*-methoxycarbonyl group *endo* to the condensed ring system (Scheme 1). In addition small amounts of the diastereomeric **3a** and unchanged **1a** are present. In a preceding paper of this series[1] we reported that addition of trifluoroacetic acid anhydride (TFAA) to this solution afforded the two corresponding *N*8-trifluoroacetyl derivatives **2b** and **3b** in addition to a small amount of **1b**. The acylating agent is believed to be an ion pair between the protonated TFAA and the trifluoroacetate ion reacting in a stepwise mechanism by way of the trifluoroacetylium ion.[2–5]

In contrast with these findings trifluoroacetylation of the same compound (**1a**) in dry pyridine takes a completely different path forming a complex reaction mixture. The main constituents are the dihydropyridyl adduct **4** (ca. 50%), the N_a-trifluoroacetylated tryptophan **1b** (ca. 5%) and a mixture of two diastereomeric 2,3-dihydrotryptophans **5a**/**b** (ca. 10%) (Scheme 2). The identity of **4** was derived from a single crystal X-ray structural determination.[6] The gross structures of the diastereomeric **5a** and **5b** were inferred from the presence of the expected molecular ions, NMR signals from a pertubed side chain, the four aromatic protons and a proton which according to the downfield chemical shift (see Table 1) must be connected to position 2. The presence of a hemiaminal carbon atom (2′) revealed itself as a quartet (**5a**, **5b** δ 93.0) in the noise-decoupled ^{13}C spectrum exhibiting long-range couplings (**5a**, **5b** $^2J_{CF}$ =



Scheme 1.

† Part IV, see Ref. 8.
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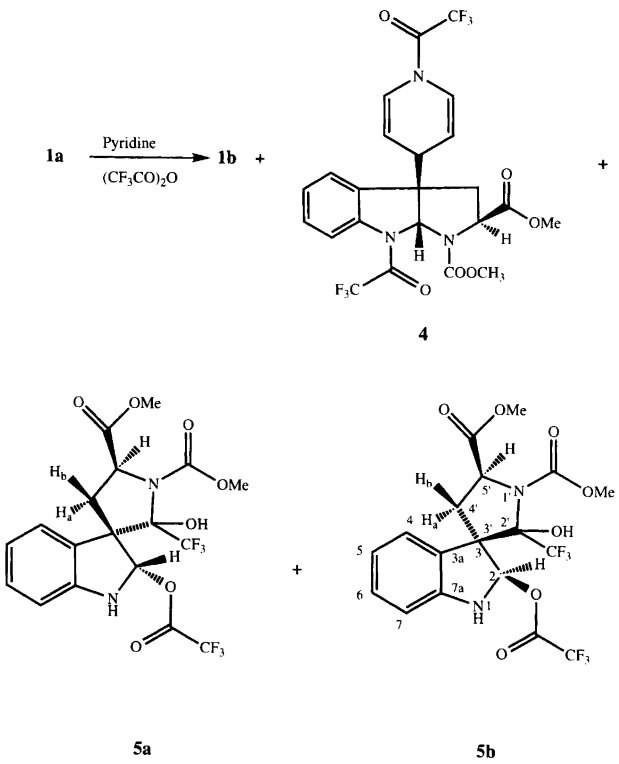

Scheme 2.

31–32 Hz) to the fluorine atoms. An inverse long-range CH correlation experiment optimized for $^3J_{CH}$ 10 Hz revealed connectivities between H(2) and C(2′), C(3a), C(7a) and between H(4′) and C(2), C(2′), C(3′) and C(5′). Furthermore, a long-range NH correlation experiment indicated connectivity between H(4′) and N(1′).

The absolute stereochemistry was tentatively assigned based on the known *S* configuration of the 5′ center and on NOE results. In **5b** no NOE enhancement was observed between the proton at position 2 (δ 6.48) and the one at position 5′ (δ 4.55), while in **5a** an enhancement in the signal of H(2) resulted from saturating H(5′) (δ 4.51) and also in the reverse experiment. In the latter case (**5a**) the H_b (*pro-S*) proton was identified as the one appearing at δ 2.45 because of an enhancement of this signal on irradiation of H(2) at δ 6.09. By inspection of molecular models these results are only compatible with a 2*R*,3*R*,5′*S* configuration of **5b** and 2*S*,3*S*,5′*S* of **5a**. These assignments where the two stereocenters 2 and 3 close to the phenylic chromophore are mirror images of each other are supported by the CD curves, which are virtually mirror images for the two compounds. The absolute stereochemistry at the 2′ center was not determined. Even though this stereocenter represents a hemiacetal analogue we believe that epimerization does not occur under the conditions of the rotation experiment since mutarotation was not detected.

The presence of **1b** in the reaction mixture can be accounted for as a result of trifluoroacetylation of **1a**. Failure of **1b** to react with TFAA in pyridine precludes this compound as an intermediate in the formation of **4**.

The formation of **4** and **5** requires further elaborate mechanisms. The reaction pathway may be envisaged

Table 1. ^{1}H and ^{13}C NMR assignments of **5a** and **5b**.

	5a[a]		**5b**[b]	
Position	δ_H J_{HH}/Hz	δ_C	δ_H $J_{H,H}$/Hz	δ_C
1	3.53br		3.03br	
2	6.09	85.4	6.48 3.1	85.7
3=3′		60.4		60.2
3a		125.7		126.2
4	7.26 7.7	125.6	7.30 7.7	125.3
5	7.16 7.4	126.0	7.22 7.5, 1.0	125.7
6	7.34 7.8	130.4	7.40 7.7, 8.0	130.3
7	8.00 8.1	118.6	8.08 8.0	118.5
7a		140.8		140.9
5′	4.51 10.4, 8.0	57.7	4.55 9.9	57.8
4′	2.94 (H_a) 13.6, 7.9 2.45 (H_b) 13.0, 11.2	28.8	2.90 (H_a) 14.5, 10.4 2.72 (H_b) 14.5	28.8
2′		93.0		93.5
*Me*OCON	3.75	52.6	3.81	53.0
MeO*C*ON		155.2		155.7
*Me*OCO	3.73	53.6	3.77	53.3
MeO*C*O		170.4		172.2
OH	6.70		6.88	

The assignments of the spin–spin splittings observed were confirmed from COSY data and the C–H correlations from HETCOR data. [a]The trifluoroacetoxy group of **5a** appeared at δ 122.7 ($^1J_{CF}$=291 Hz) and δ 153.7 ($^2J_{CF}$=38 Hz) and the trifluoromethyl group and the connected hemiaminal at δ 116.0 ($^1J_{CF}$=288 Hz) and δ 93.0 ($^2J_{CF}$=31 Hz), respectively. [b]The corresponding values observed in **5b** were δ 123.2 (q, $^1J_{CF}$=292 Hz), δ 153.9 (q, $^2J_{CF}$=38 Hz) and δ 116.0 (q,$^1J_{CF}$=288 Hz), δ 93.0 (q, $^2J_{CF}$=32 Hz).

as comprising an initial electrophilic attack of activated TFAA on the indole 3-position forming an 3-trifluoroacetylindolium ion. TFAA in pyridine has recently been shown to exist in an equilibrium mixture as free TFAA and a 1:1 dipolar adduct with pyridine.[7] This complex is believed to be responsible for the enhanced reactivity of TFAA in pyridine and may well be active in transferring the trifluoroacetyl group to the 3-position leaving trifluoroacetate ion to attack at the 2-position. Eventually nucleophilic attack of the N_b lone pair at the trifluoroacetyl carbonyl group generates the spiro-connected L-proline ring. Analogously, in the case of **4** the initial attack at the indole 3-position occurs through the electrophilic 4-position of the pyridine trifluoroacetic anhydride complex. Concurrently with this attack, the complex eliminates the trifluoroacetate ion generating an 2-indolenium ion. The latter species suffers nucleophilic attack by the N_b amide nitrogen to give the protonated form of **4**. Clearly, in order to draw firm conclusions regarding the reaction mechanisms operating, more data are needed.

Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 250 or on a Varian UNITY 400 spectrometer, operating at 250 or 400 MHz for protons and at 62.9 or 100.6 MHz for carbons, respectively. The inverse experiments were performed on a Bruker 600 spectrometer. All spectra were recorded in $CDCl_3$ which was also used as an internal standard. Mass spectra were obtained on a Masslab VG20–250 quadrupole or a JEOL JMS-HX/HX-110A spectrometer using the direct inlet system. Melting points were determined on a Büchi 535 apparatus and are uncorrected. Analytical HPLC was carried out on an LKB-Pharmacia gradient system equipped with a Hewlett-Packard photodiode array detector using Hibar (Merck) RP 18 columns (MeCN–H_2O). The preparative separations were performed with a Merck Lobar system using LiChroprep Si 60 (EtOAc–heptane). All solvents were distilled prior to use. L-Tryptophan methyl ester hydrochloride, TFA and TFAA were from Aldrich.

Trifluoroacetylation of N_b*-methoxycarbonyl-*L*-tryptophan methyl ester* (**1a**). To a solution of **1a** (1 g, 3.62 mmol) in dry pyridine (30 ml, dried over Linde 4 Å molecular sieves, water content 15.8 ppm according to a Karl Fisher determination) was added TFAA (2.5 ml). After being stirred for 30 min in an ice bath, the reaction mixture was concentrated *in vacuo* and ice–water was added. The major amount of pyridinium trifluoroacetate was vaporized by freeze drying. TLC on silica gel with 25 and 30% AcOEt in heptane showed the presence of at least 7 different compounds including the starting material. Column chromatography on silica gel with different ratios of AcOEt–heptane as the eluent gave rise to the four products described below. Attempted reaction of **1a** in triethylamine with an excess of TFAA resulted only in decomposition of the triethylamine and recovery of starting material.

N_a - *Trifluoroacetyl* - N_b - *methoxycarbonyl* - L - *tryptophan methyl ester* (**1b**). Recrystallized from AcOEt–heptane 1:1. Homogenous according to HPLC analyses (RP C-8, H_2O–MeCN with a gradient of 10–100% MeCN). Yield 3–5%. M.p. 119 × 120 °C. Anal. $C_{16}H_{15}F_3N_2O_5$: C, H, N. MS *m–z* 372 (M^+). Attempted reaction of **1b** in pyridine with TFAA only resulted in the isolation of starting material.

*(2S,3aR,8aS) - 3a - (*N *- trifluoroacetyl - 1,4 - dihydro - 4 - pyridyl) - 1,2 - bis(methoxycarbonyl) - 8 - trifluoroacetyl - 1,2,3,3a,8,8a - hexahydropyrrolo [2,3 - b] indole* (**4**). Recrystallized from EtOH. Homogenous according to HPLC analyses (conditions as above). Yield ca. 50%. M.p. 178–179 °C (by differential scanning calorimetry 186 °C). Anal. $C_{23}H_{19}F_6N_3O_6$: C, H, N. MS *m–z* 547.1179 (Δ mmu 0.1).

(2S,3S,5'S) - 2,3 - Dihydro - 2 - trifluoroacetoxy - 1',5' - bis-(methoxycarbonyl) - 2' - hydroxy - 2' - trifluoromethylspiro [indole-3,3'-pyrrolidine] **5a**. Yield around 5%, m.p. 143–144 °C. UV [abs. EtOH (log ε)] nm 214 (sh, 4.09), 255 (3.79), 278 (sh, 3.44), 285 (sh, 3.30). $[\alpha]_D^{20}$ −36.3° (*c* 0.01, EtOH). CD [EtOH, $c = 2.12 \times 10^{-3}$ M] nm (Δε) 220 (7.3), 258 (2.7), 280 (−0.5), 286 (−1.2). MS [E_i 70 eV; *m–z* (% rel. int.)] 486 (10, M^+), 365 (15), 324 (17), 297 (100), 226 (60), 130 (13).

(2R,3R,5'S) - 2,3 - Dihydro - 2 - trifluoroacetoxy - 1',5' - bis-(methoxycarbonyl) - 2' - hydroxy - 2' - trifluoromethylspiro-[indole-3,3'-pyrrolidine] **5b**. Yield around 5%, m.p. 116–118 °C. UV [MeOH (log ε)] nm 253 (4.07), 278 (sh, 3.73), 285 (sh, 3.58). $[\alpha]_D^{20}$ −36.3° (*c* 0.51, MeOH). CD [MeOH, $c = 1.07 \times 10^{-5}$ M] nm (Δε) 221 (20.3), 259 (−6.0), 280 (0.8), 289 (2.1). The mass spectrum was virtually identical with that reported for **5a**.

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