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Short Communication

Cyclisations of Tryptophans. I. Trifluoroacetylation of N_b-Methoxycarbonyl-L-tryptophan Methyl Ester in Trifluoroacetic Acid

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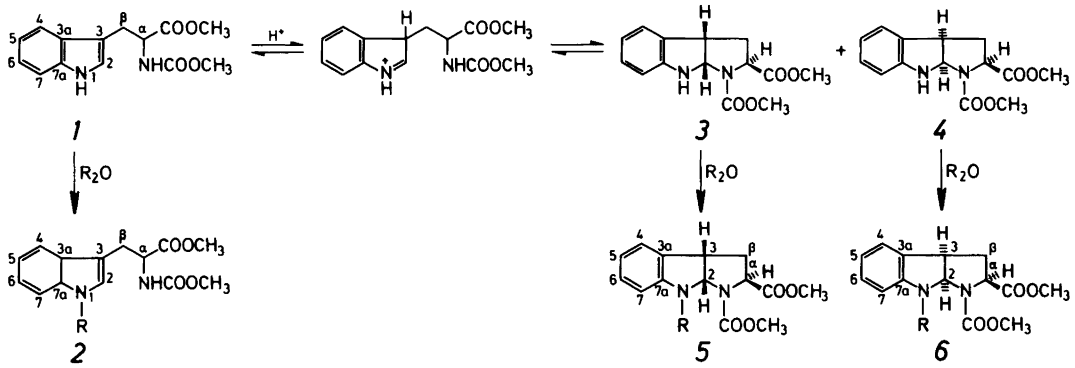
Hino and Tanaguchi[1,2] reported that cyclisation of N_b-methoxycarbonyl-L-tryptophan methyl ester (**1**) in trifluoroacetic acid (TFA) proceeds via the stepwise mechanism outlined in Scheme 1. Initial protonation of **1** at the indole 3-position is followed by fast cyclisation to give the diastereoisomeric, cyclic tautomers **3** and **4**. Subsequent treatment with acetic anhydride converts **3**/**4** into the more stable acetyl derivatives **5a**/**6a**. While **3** is the kinetically favoured product (ratio **4**/**3** = 0.05 after 3 min at 15°C), **4** is the thermodynamically stable isomer (ratio **4**/**3** = 4.3 after 60 min). By using appropriate reaction conditions[3–6] the stable isomer **4** and derivatives of **4** can be obtained free of contamination with isomeric compounds. Although in TFA the cyclic tautomers **3**/**4** and **5a**/**6a** are predominant, **5** (R = benzenesulfonyl), regenerates the open tautomer **2** (R = benzenesulfonyl) in five minutes at room temperature.[5] This was attributed to the electronegativity of the sulfonamide group[3] which reduces the tendency of the indole nucleus to undergo the protonation of C-3 necessary for cyclisation.[2]

Here we describe the products obtained by addition of trifluoroacetic anhydride to an equilibrated solution of **1** in TFA. In addition to the cyclic **6b** (84% yield), **5b** (6% yield), and unchanged **1** (1%), a 5% yield of the trifluoroacetylated open-chain isomer **2b** was isolated. The ratio **6b**/**5b** = 17 after 4 h indicates preferential formation of the thermodynamically stable isomer **6b** in harmony with the results obtained on acetylation. Since NMR experiments established that **2b** is stable in TFA, the latter compound must be formed in an essentially irreversible reaction probably from the small amounts of **1** present at equilibrium. It is noteworthy that the electronegativity of the trifluoroacetyl group is insufficient for forming the open-chain isomer **2b** as observed for sulfonylated derivatives in TFA.

The ^1H and ^{13}C NMR spectra were assigned in the



Scheme 1. **a**: R = CH_3CO **b**: R = CF_3CO

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Table 1. ^1H and ^{13}C chemical shifts (δ) and coupling constants (J/Hz) for **1**, **2b**, **5b** and **6b**.

	1		**2b**		**5b**		**6b**	
Atom No.	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
2	6.98 s	122.7	7.28 s	126.5[a]	6.45 d (5.8)	76.7	6.53 d (6.0)	76.7
3		111.1		117.0	4.08 dd (5.8, 9)	46.1	4.07 dd (6.0, 6)	45.3
3a		127.3		130.4		131.7		131.2
4	7.53 dd (7, 1)	118.4	7.54 dd (7, 1)	116.9	7.27 d (7)	123.8	7.16 d (7)	125.7
5	7.18 td (7, 1)	122.0	7.43 td (7, 1)	125.5[a]	7.21 t (7)	126.4	7.19 t (7)	124.1
6	7.11 td (7, 1)	119.5	7.32 td (7, 1)	119.1	7.32 t (7)	129.1	7.29 t (7)	128.6
7	7.33 dd (7, 1)	111.1	8.41 dd (7, 1)		8.05 d (7)	118.7	8.00 d (7)	118.1
7a		136.0		135.9		141.2		141.0
α	4.70 dd (5.5, 7.5)	54.3	4.74 dd (6.8, 5.6)	53.5	4.04 dd (7.2, 9.6)	59.1	4.50 d (8)	58.1
β	3.29 d (5.5)	27.8	3.20 dd (5.6, 14.8)	27.9	2.35 ddd (9, 9.6, 17)	31.7	2.62 ddd (6, 8, 13)	32.5
			3.29 dd (5.6, 14.8)		2.70 dd (7.2, 17)		2.72 d (13)	
$COOCH_3$		172.4		171.6		172.2		170.8
$COOCH_3$	3.67 s	52.2	3.70 s	52.5	3.74 s	52.5[a]	3.09 s	52.0
NH	8.15 s, 5.23 d (7.5)		5.36 d (6.8)					
$NCOOCH_3$		156.3		156.2		154.1		154.3
$NCOOCH_3$	3.65 s	52.2	3.68 s	52.5	3.64 br s	52.9[a]	3.70 br s	52.9
$COCF_3$				115.5		116.7		116.0

[a] May be interchanged.

usual way (COSY, DEPT, HETCOR) as shown in Table 1. The two β protons in **5b** could be assigned by means of NOE difference spectroscopy. Irradiation at the signal at 2.35 ppm gave rise to 5% enhancement of the signal attributed to the proton at position 3 indicating these two protons to be *cis*. The other β proton (2.70 ppm) as expected was spatially close to the α proton (14% enhancement) but also to some of the aromatic protons (1–2% enhancement). The *cis* fusion of the two five-membered rings was confirmed by a 3% enhancement of the signal from the proton at position 3 by irradiation of the resonance frequency of the proton at position 2. The cyclic tautomers could be distinguished by the position of the Me signal of the ester group appearing at lower field (3.74 ppm) in **5b** than in the diastereomeric **6b** (3.09 ppm) in analogy to the findings of Hino[2] for the acetyl derivatives **5a** and **6a**. In the corresponding sulfonylated derivatives (e.g., **5**, R = tosyl)[3] slow rotation around both the N–COOMe and N–tosyl bonds resulted in considerable broadening of spectral lines at room temperature. The ^1H NMR spectrum of **5b** and **6b** in $CDCl_3$ at 50°C gave no indication of *cis–trans* isomerism. However, at lower temperatures (23°C) considerable broadening of the bands originating from the protons at the carbamate methyl group, the α position, and position 7 occurred. These trends were paralleled in the carbon spectra where the signals from carbon atoms at positions α, β, 2, and 3 were very broad at ambient temperature but sharp at 50°C. On cooling a solution of **5b** in $CDCl_3$ to 0°C the 7-H signal appeared as two doublets at 7.99 and 8.11 ppm in the ratio 42 : 58. These changes are attributed to hindered rotation around the C–N bond of the N–$COCF_3$ and the N–COOMe group.

Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Bruker 250 AM or on a Varian XL-400 spectrometer, operating at 250 or 400 MHz for protons and at 62.9 or 100.6 MHz for carbons, respectively. All spectra are recorded for solutions 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/HX110A spectrometer using the direct inlet system. Melting points were determined on a Büchi 535 apparatus and are uncorrected. Analytical HPLC was carried out on a LKB-Pharmacia gradient system equipped with a Hewlett Packard photodiode array detector using Hibar (Merck) RP 18 columns (acetonitrile–water). 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* (**1**). An equilibrated solution of **1**[7] (1 g, 3.6 mmol) in TFA (15 ml) was stirred at room temperature and an excess TFAA (2.3 g, 10.8 mmol) added over a period of 5 min with occasional cooling. Stirring was continued for another 4 h at room temperature. The mixture was taken to dryness *in vacuo* to leave a yellow oil which was purified by column chromatography to furnish three pure compounds, 4% unidentified product and 1% recovered starting material.

N_b*-Methoxycarbonyl-*N_a*-trifluoroacetyl-*L*-tryptophan methyl ester* (**2b**). Yield 61 mg (5%), m.p. 119–120°C. Anal. $C_{16}H_{15}F_3N_2O_5$: C, H, N. MS [*E* 70 eV; *m/z* (% rel. int.)] 372 (36, M^+), 297 (97, $M^+ - NH_2COOCH_3$), 226 (100, $M^+ - CH_3OOCCHNHCOOCH_3$).

*Dimethyl (2*S*,3a*S*,8a*R*)-8-trifluoroacetyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate* (**5b**). Yield 79 mg (6%), m.p. 122–123°C. Anal. $C_{16}H_{15}F_3N_2O_5$: C, H, N. MS 372 (100, M^+), 313 (88, $M^+ - COOCH_3$).