

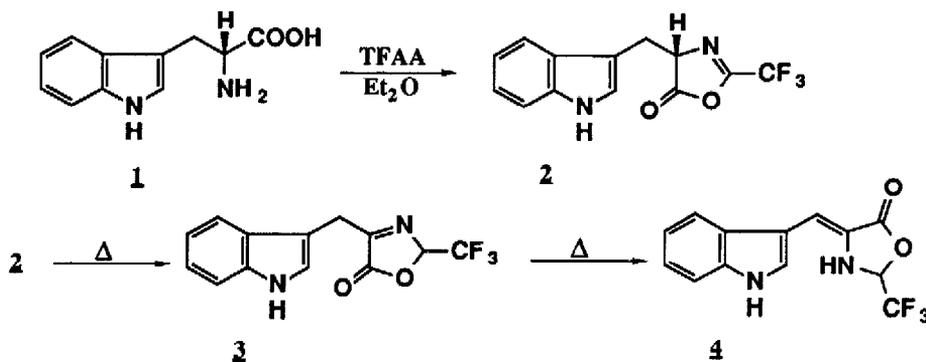
REACTION OF TRYPTOPHAN WITH TRIFLUOROACETIC ANHYDRIDE

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Abstract: Trifluoroacetic anhydride (TFAA) in ether quickly (= 5-10 min) converted tryptophan to the crystalline 2-trifluoromethyl-5(4H)-oxazolone (2) without racemization. Dissolution of optically active 2 in acetonitrile gave racemic 2, whereas treatment with hot aqueous dioxane gave the isomeric oxazolone (3). Both 2 and 3, could on heating be further isomerized to the conjugated oxazolone (4). These oxazolones are interesting starting materials for the preparation of tryptophan containing peptides.

Weygand and Steglich have, in series of papers^{1,2} reported on the reaction of amino acids and trifluoroacetic anhydride (TFAA). Initially formed 2-trifluoromethyl-5(4H)-oxazolones readily isomerized^{3,4} to 2-trifluoromethyl-5(2H)-oxazolones. This type of protected and activated derivative has only found limited interest for the preparation of dipeptides due to racemization associated with isomerization.⁵ We have now found that tryptophan (1) when added to a solution of TFAA in ether at 30°C quickly dissolves, and within 5-10 minutes the 5(4H)-oxazolone (2) crystallises in 90% yield without racemization⁶. In comparison, the previously reported^{5,7} conditions, heating of amino acids in TFAA+TFA, gave racemic N-trifluoroacetyltryptophan and in fact only aspartic acid, glutamic acid and proline gave products with retained optical activity.⁵

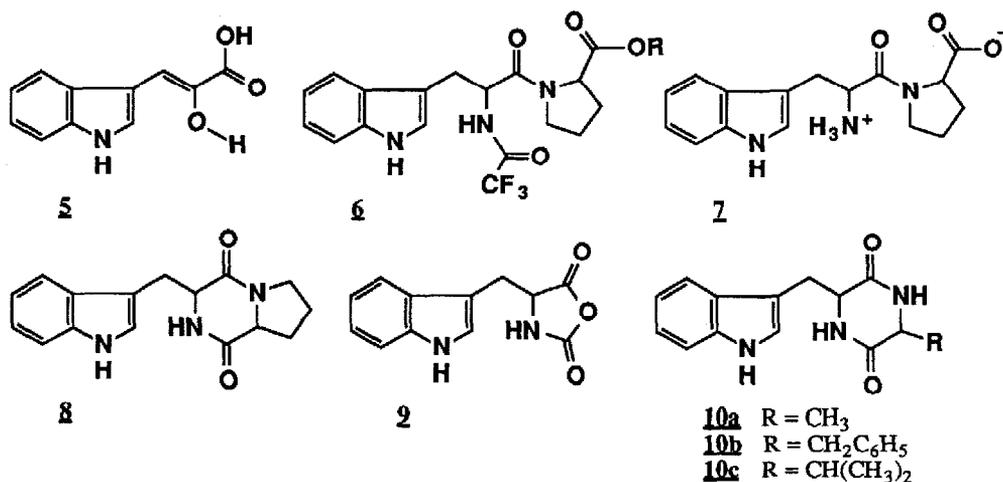


Dissolution of **2** in acetonitrile at 23°C resulted in racemization ($t_{1/2} = 40$ min), presumably *via* a keto-enol tautomerization (*cf* ref.8). No side-reactions involving ring-opening were observed during this operation. Isomerization of **2** to **3** could be accomplished in 80% yield by heating **2** in aqueous dioxane (100°) for a few minutes. Heating (110°C, 12h) of **2** or **3** (neat) resulted in isomerization to the conjugated oxazolone **4** ($\approx 40\%$ yield), i.e. a protected derivative of dehydrotryptophan (Δ Trp), the latter being of importance as a component in e.g. telomycine and as starting material for asymmetric syntheses.⁹ The isomers (**2,3** and **4**) were further characterized by IR and NMR studies¹⁰⁻¹² and conversion into derivatives.

Acid hydrolysis (1% HCl in H₂O-MeOH) of **2** or **3** gave N-trifluoroacetyltryptophan¹³ whereas mild alkaline hydrolysis (OH⁻, H₂O, EtOH, ≈ 10 min/ 10°C) followed by acidification proved to be a quick (≈ 30 min) and convenient high-yielding (> 90%) preparative method of the notoriously unstable^{14,15} indole-3-pyruvic acid (**5**). Similar hydrolytic cleavages of other oxazolones to pyruvic acids had previously been reported by Weygand and Steglich¹⁶ as well as by Coscia.¹⁷

The 2-trifluoromethyl-5(4H)-oxazolone **2** was readily ring-opened under mild conditions by e.g. esters of proline, which gave the protected dipeptide **6**. Hydrolysis (OH⁻, H₂O, ROH) of **6** gave the amino acid **7** rather than the expected cyclo-dipeptide **8**. This result indicates that the HNCOCF₃ group is more resistant towards alkaline hydrolysis than the ester group.¹⁸ The amino acid **7** was readily cyclized by DCC to give **8**. Cyclization effected by thermolysis gave *epi*-**8** (L-D) a result in line with previous studies by Sammes¹⁹ and Liberek.²⁰

For comparison the known²¹⁻²³ but hard-to-make compound **9** was prepared. Compound **9** reacted quickly and smoothly with methyl proline yielding the cyclopeptide **8** directly. However, due to the ready availability of **2** this method seems, in spite of the problems with the removal of the COCF₃-group, to be more suitable than the NCA-method (*cf* ref. 23). This was further substantiated in the preparation of cyclo-L-Ala-L-Trp (**10a**), cyclo-L-Phe-L-Trp (**10b**) and the natural product cyclo-D-Val-L-Trp (**10c**), (*cf* refs. 24-26), from **2** and suitable esters as the reacting partner.



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10. Compound 2: $[\alpha]_D^{25} = -183.2$ (c. 1.14, EtOAc). mp. $\approx 100^\circ\text{C}$ (dec). IR(KBr): 3318, 1859, 1694, 1388, 1190(br), 1069, and 755cm^{-1} . $^{13}\text{C-NMR}$ (CDCl_3): 174.1(s), 153.5(N=C), 135.9(s), 126.9(s), 123.6(d), 122.5(d), 119.9(d), 118.9(d), 111.1(d), 107.9(s), 66.3(d), and 26.5(t) ppm.
11. Compound 3: mp. $96-98^\circ\text{C}$. IR(KBr): 3380, 1795, 1185(br), 1158, 1097, 1022, 873, 750, and 709cm^{-1} . $^{13}\text{C-NMR}$ (CDCl_3): 166.7(s), 163.8(s), 136.2(s), 126.8(s), 124.4(d), 121.2(d), 120.8(q, CF_3), 118.6(d), 118.4(d), 111.5(d), 105.8(s), 92.0(q, CH- CF_3), and 24.4(t) ppm.
12. Compound 4: mp. 165°C (dec). IR(KBr): 3408, 3301, 1759, 1650, 1325, 1248, 1180(br), 1038, 858, 757, and 692cm^{-1} . $^{13}\text{C-NMR}$ (DMSO-d_6): 166.5(s), 135.9(s), 126.8(d), 126.4(s), 122.4(q, CF_3), 122.3(d), 121.3(s), 120.0(d), 118.4(d), 111.9(d), 109.8(s), 103.8(d), and 82.4(q, CH- CF_3) ppm.
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