Tetrahedron Letters,Vol.30,No.34,pp 4597-4600,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

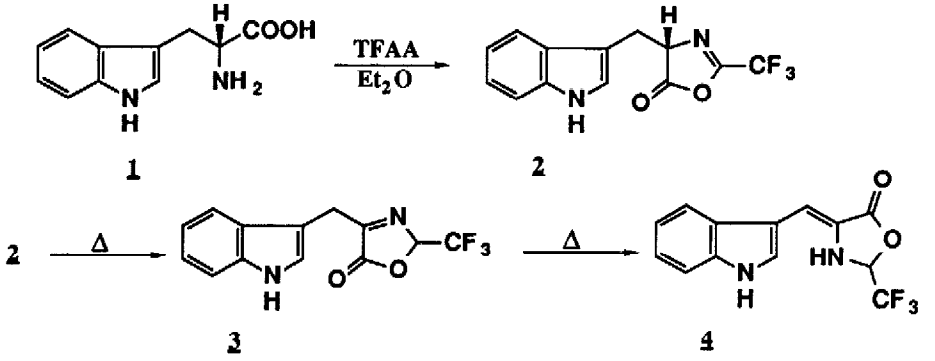
REACTION OF TRYPTOPHAN WITH TRIFLUOROACETIC ANHYDRIDE

Jan Bergman* and Göran Lidgren

Department of Organic Chemistry, Royal Institute of Technology,
S-100 44 Stockholm, Sweden.

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 racemization[6]. 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]



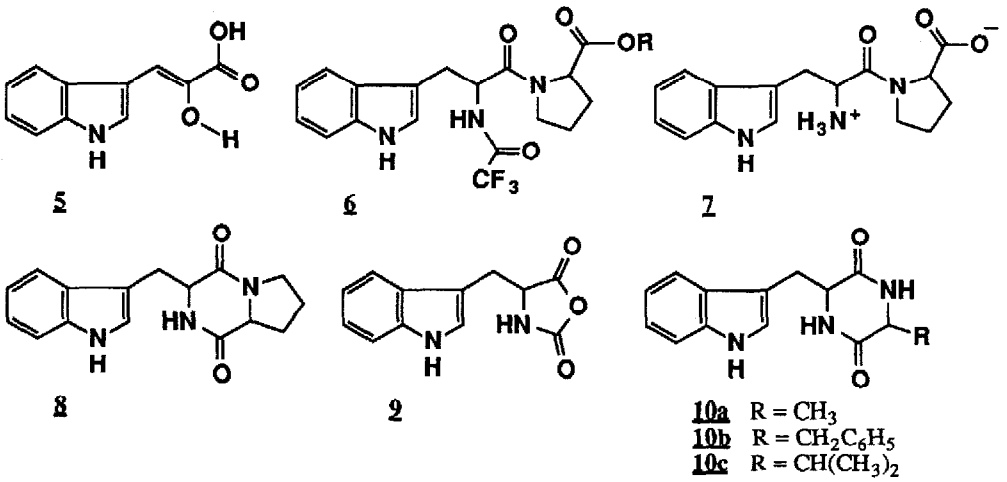
1 **2** **3** **4**

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** (≈40% yield), i.e. a protected derivative of dehydrotryptophan (ΔTrp), 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 studies[10-12] and conversion into derivatives.

Acid hydrolysis (1% HCl in H_2O-MeOH) of **2** or **3** gave N-trifluoroacetyltryptophan[13] whereas mild alkaline hydrolysis (OH^-, H_2O, 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 Steglich[16] 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^-, H_2O, ROH) of **6** gave the amino acid **7** rather than the expected cyclo-dipeptide **8**. This result indicates that the $HNCOCF_3$ group is more resistent 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 Sammes[19] and Liberek.[20]

For comparison the known[21-23] but hard-to-make compound **9** was prepared. Compound **9** reacted quickly and smoothly with methyl prolinate 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 $COCF_3$-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.



Acknowledgements

The authors wish to express their sincere gratitude to Degussa AG, Frankfurt, BRD, for a most generous gift of tryptophan.

REFERENCES AND NOTES

1. F. Weygand, G. Klipping, and D. Palm, *Chem. Ber.* **93**, 2619 (1960) and previous papers in this series.
2. V. Austel, and W. Steglich, *Chem. Ber.* **108**, 2361 (1975) and previous papers in this series.
3. W. Steglich, *Fortschr. Chem. Forsch.* **12**, 77 (1969).
4. R. Cotton, P.M. Hardy, and A.E. Langran-Goldsmith, *Int. J. Peptide and Protein Res.* **28**, 230 (1986).
5. F. Weygand, and R. Geiger, *Chem. Ber.* **89**, 647 (1956).
6. The *ee* was > 97% as determined by PMR of the product with L-α-phenylethylamine.
7. F. Weygand, and A. Röpsch, *Chem. Ber.* **92**, 2095 (1959).
8. M. Slebioda, M.A. St-Amand, F.M.F. Chen, and N.L. Benoiton, *Can. J. Chem.* **66**, 2540 (1988). and refs. therein.

9. T. Moriya, N. Yoneda, M. Miyoshi, and K. Matsumoto, *J. Org. Chem.* **47**, 94 (1982). and refs. cited therein.
10. Compound **2**: $[\alpha]_D$= -183.2 (c. 1.14, EtOAc). mp.≈100°C (dec). IR(KBr): 3318, 1859, 1694, 1388, 1190(br), 1069, and 755cm^{-1}. ^{13}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°C. IR(KBr): 3380, 1795, 1185(br), 1158, 1097, 1022, 873, 750, and 709 cm^{-1}. ^{13}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 692 cm^{-1}. ^{13}C-NMR ($DMSO_{d6}$): 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.
13. W. Steglich, and S. Hinze, *Synthesis*, 399 (1976).
14. K.N.F. Shaw, A. McMillan, A.G. Gudmundson, and M.D. Armstrong, *J. Org. Chem.* **23**, 1171 (1958).
15. G. Nazario, and K. Schwartz, *Arch. Biochem. Biophys.* **123**, 457 (1968).
16. F. Weygand, W. Steglich, and H. Tanner, *Ann. Chem.* **658**, 128 (1962).
17. M.L. Wilson, and C.J. Coscia, *J. Org. Chem.* **44**, 301 (1979).
18a. Attempted ammonolysis gave similar problems (*cf.* ref. 18b).
18b. E.G. Breitholle, and C.H. Stammer, *J. Org. Chem.* **41**, 1344 (1976).
19. P.G. Sammes, and A.C. Weedon, *J. C. S. Perkin I*, 3048 (1979).
20. B. Liberek, A. Chodup, A. Kitowska, and M. Kozlowska, *Roczniki Chemii* **48**, 2075 (1974).
21. A. Patchornik, M. Sela and E. Katchalski, *J. Am. Chem. Soc.* **76**, 299 (1954).
22. G.D. Fasman, M. Landsberg and M. Buchwald, *Can. J. Chem.* **43**, 1588 (1965).
23. J.A. Nagy, S.P. Powers, B.O. Zweifel, and H.A. Scheraga, *Macromolecules* **13**, 1428 (1980).
24. E. Houghton and J.E. Saxton, *J. Chem. Soc. (C)*, 1003 (1969).
25. C.M. Maes, M. Potgeiter and P.S. Steyn, *J. Chem. Soc. Perkin Trans I*, 861 (1986).
26. R.D. Stipanovic, H.W. Schroeder and H. Hein, Jr., *Lloydia* **39**, 158 (1976).

(Received in UK 10 July 1989)