FUNCTIONALIZATION AT C-3a OF TRYPTOPHAN DERIVED HEXAHYDROPYRROLO[2,3-*b*]INDOLES

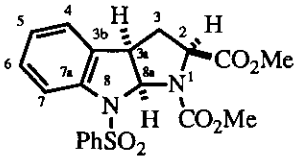
Milan Bruncko, David Crich*, and Raghu Samy

University of Illinois at Chicago, Department of Chemistry (M/C 111), 801 W.
Taylor St., Chicago, IL 60607-7061, USA

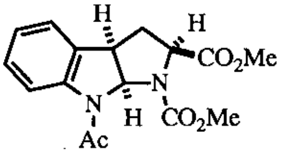
Abstract- Under free radical conditions the cyclic tryptophan tautomer (**1**) suffers oxidation at the benzylic position (C-3a) giving, with NBS, the 3a-bromo derivative and, with CAN, the 3a-hydroxy and 3a-nitrato derivatives. In contrast, under electrophilic conditions, aromatic bromination with NBS occurs cleanly at C-5.

In continuation of our studies on the chemistry, and use in asymmetric synthesis, of cyclic tautomers of tryptohan[1] we now report an interesting dichotomy in the oxidation of the hexahydropyrroloindole (**1**) that considerably extends the synthetic scope of this readily available chiral substrate.[2,3]

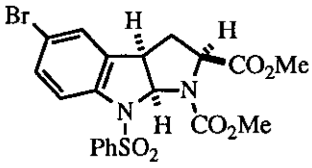
Hino reported in 1983, that the *N*-8 acetamido analogue (**2**) of **1** undergoes clean bromination, with *N*-bromosuccinimide (NBS) in acetic acid, and nitration with HNO_3/H_2SO_4 at C-5.[4,5] In full agreement with Hino we find that **1**, on reaction with NBS in acetic acid provides the 5-bromo derivative (**3**) cleanly and in 90 % yield. The regiochemistry of this reaction was confirmed by n.O.e. difference spectroscopy which revealed the proximity of H-3a and H-3endo to the *meta*-doublet assigned as H-4.



1

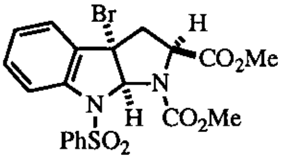


2

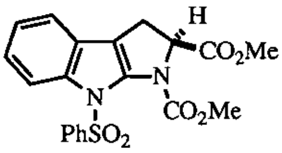


3

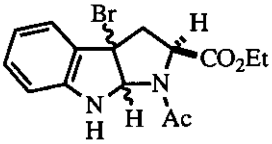
In contrast, heating **1** to reflux in tetrachloromethane with NBS results in clean benzylic bromination and isolation of **4** in 72 % yield at approximately 92 % conversion.[6] The reaction is best stopped at this stage as any attempt to drive the reaction to completion results in further reaction at C-2 and ultimately in lower yields. The bromide (**4**) is an off white crystalline solid, stable in air for many months at room temperature. Most importantly, it shows no tendency to undergo elimination to the dehydro product (**5**). This stability is to be contrasted with the instability of **6**, formed by treatment of *N*-acetyltryptophan methyl ester with NBS, that undergoes very rapid elimination of HBr with formation of **7** as reported by Witkop.[7]



4

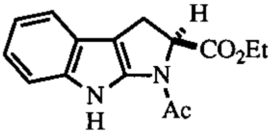


5

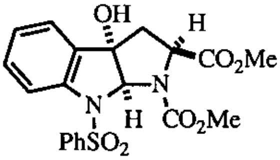


6

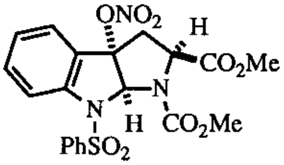
Reaction of **1** with ceric ammonium nitrate (CAN) in aqueous acetonitrile at room temperature similarly resulted in benzylic oxidation with the clean formation of mixtures of the alcohol (**8**) and the nitrate ester (**9**),[8] in approximately 65 % combined isolated yield, with the exact composition of the product mixture depending on the ratio of H_2O/MeCN/CAN employed.[9] As with the bromination, the CAN oxidation was best stopped before completion to ensure the absence of over oxidation products. The nitrate ester (**9**) could be cleanly reduced to the alcohol (**8**) by tributyltin hydride in benzene at reflux.[10]



7

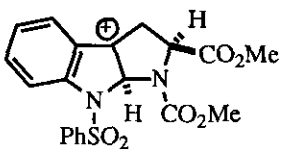


8

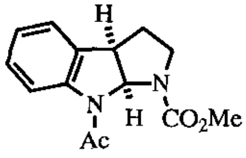


9

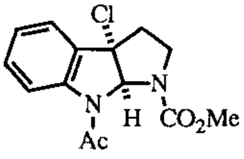
Like the bromide (**4**), both **8** and **9** are air stable compounds showing no tendency to undergo elimination to the indole (**5**). Indeed, the stability of **4** and **9** is such that in typical 70 eV EI mass spectra they exhibit molecular ions of relative intensities 6 and 5 % respectively and the principal mode of fragmentation of their molecular ions does not involve loss of the heteroatom from C-3a. The reluctance of **4**, **8** and **9** to undergo elimination, coupled to the evident stability of the molecular ions of **4** and **9**, is suggestive of a relatively high energy for the cation (**10**) which might derive from its inability to achieve planarity and so optimum overlap with the aromatic ring and/or the strongly electron withdrawing effect of the sulfonyl group. At this stage we note that Hino recorded the formation of **12** in 21 % yield as a byproduct on treatment of **11** with *N*-chlorosuccinimide (NCS) in acetic acid but, in the absence of any revealing substituent at C-2, considered that this product was formed by ring opening of **11** to the tryptamine tautomer followed by attack of NCS at the indole 3-position and reclosure onto the so-formed indolenium ion.[4] It is evident that such a mechanism is not operative in the present case as **4** was isolated free from contamination by its diastereoisomer (**13**).



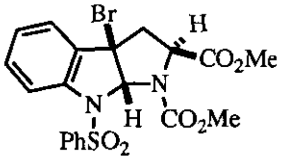
10



11



12



13

Whatever the reason for the stability of **4**, **8** and **9**, it is clear that **1** suffers attack by electrophiles at C-5 in the aromatic ring whereas under radical conditions it is the benzylic position (C-3a) that is functionalized. The ready formation of these C-3a functionalized derivatives, as single enantiomers and diastereoisomers, opens up the attractive possibility of the asymmetric synthesis of a number of hexahydropyrrolo[2,3-*b*]indole alkaloids[11] and oxidative metabolites[12] of tryptophan. Progress in this direction will be reported in due course.

ACKNOWLEDGEMENTS

We thank the University of Illinois at Chicago for support and for a fellowship to M. B..

REFERENCES

1. D. Crich and J. W. Davies, *J. Chem. Soc., Chem. Commun.*, 1989, 1418; G. T. Bourne, D. Crich, J. W. Davies, and D. C. Horwell, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1693; C.-O. Chan, C. J. Cooksey, and D. Crich, *J. Chem. Soc., Perkin Trans. 1*, 1992, 777; C.-O. Chan, D. Crich, and S. Natarajan, *Tetrahedron Lett.*, 1992, **33**, 3405; D. Crich, C-O. Chan, J. W. Davies, S. Natarajan, and J. G. Winter, *J. Chem. Soc., Perkin Trans. 2*, 1992, 2233; M. Bruncko and D. Crich, *Tetrahedron Lett.*,

1992, **33**, 3193; D. Crich and L. B. L. Lim, *Heterocycles*, 1993, **36**, 0000. Also see: D. E. Zembower, J. A. Gilbert, and M. M. Ames, *J. Med. Chem.*, 1993, **36**, 305.

2. For a review on the chemistry of cyclic tautomers of tryptophan see: T. Hino and M. Nakagawa in "The Alkaloids" Ed. A. Brossi, Academic Press, 1988, **34**, 1.
3. Compound (**1**) is commercially available from Aldrich Chemical Company, Milwaukee, WI, USA.
4. M. Taniguchi, A. Gonsho, M. Nakagawa, and T. Hino, *Chem. Pharm. Bull.*, 1983, **31**, 1856. Also see: T. Hino, U. Hideya, M. Takashima, T. Kawata, H. Seki, R. Hara, T. Kuramochi, and M. Nakagawa, *Chem. Pharm. Bull.*, 1990, **38**, 2632; R. K. Dua and R. S. Phillips, *Tetrahedron Lett.*, 1992, **33**, 29.
5. For oxidation in the aromatic ring of **2** with $Pb(OAc)_4$, or Fremy's salt, see: M. Taniguchi, T. Anjiki, M. Nakagawa, and T. Hino, *Chem. Pharm. Bull.*, 1984, **32**, 2544.
6. Based on recovered starting material the yield is 78 %.
7. M. Ohno, T. F. Spande, and B. Witkop, *J. Am. Chem. Soc.*, 1970, **92**, 343.
8. All new compounds gave satisfactory microanalytical and/or high resolution mass data. Melting points and optical rotations for **3**, **4**, **8** and **9** are as follows; **3**: foam, $[\alpha]_D$ +103 (c=1.5, $CHCl_3$); **4**: mp 70 °C, $[\alpha]_D$ +93.4 (c=0.8, $CHCl_3$); **8**: mp 188-189 °C, $[\alpha]_D$ +89.6 (c=1.0, $CHCl_3$); **9**: mp 60 °C, $[\alpha]_D$ +132.4 (c=1.2, $CHCl_3$).
9. A typical reaction in 5:1 $MeCN:H_2O$ with 5 equivalents of CAN at reflux gave 25 % of **8**, 40 % of **9** and 35 % recovered **1**.
10. For reduction of nitrate esters with Bu_3SnH see: G. D. Vite and B. Fraser-Reid, *Syn. Commun.*, 1988, **18**, 1339; R. Walton and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1991, **113**, 5791.
11. For a review see: S. Takano and K. Ogasawara in "The Alkaloids" Ed. A. Brossi, Academic Press, 1989, **36**, 225.
12. I. Saito, T. Matsuura, N. Nakagawa, and T. Hino, *Acc. Chem. Res.*, 1977, **10**, 346.

Received, 8th March, 1993