Pergamon

Tetrahedron Letters, Vol. 36, No. 47, pp. 8693-8696, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01796-8

Benzocarbapenems From Ethyl Indole-2-acetate

Thomas L. Gilchrist* and Keith Graham

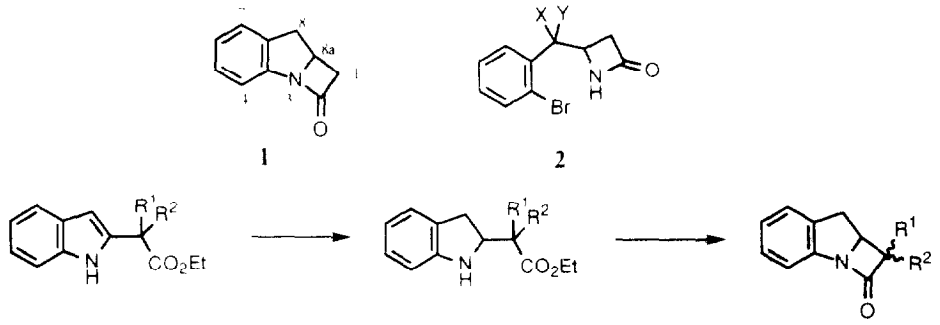
Chemistry Department, University of Liverpool, P.O. Box 147, Liverpool L69 3BX, U.K.

Steven Coulton

SmithKline Beecham Pharmaceuticals, Research Division, Brockham Park, Betchworth, Surrey RH3 7AJ, U.K.

Abstract: The benzocarbapenem **1** has been prepared from ethyl indole-2-acetate by reduction, hydrolysis of the ester and cyclisation. The methyl substituted carbapenems **12**, **13** and **14** have also been prepared. The hydrogenation of ethyl *N*-BOC-indole-2-propanoate **5** is diastereoselective.

The benzocarbapenem ring system **1**[†] has been described only once in the literature: the parent compound and two derivatives were prepared by copper promoted intramolecular aryl substitution of the azetidinones **2**.[1] We have investigated an alternative method of preparation based on the reduction and cyclisation of 2-substituted indoles, as shown in outline in Scheme 1.



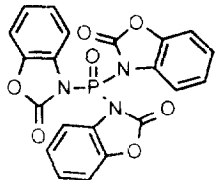
Scheme 1

The starting material required for the preparation of these azetidinones was an ester of indole-2-acetic acid. The ethyl ester has been prepared by an intramolecular Wittig reaction[2] and, more recently, the methyl ester has been prepared directly from indole by radical substitution.[3] In our hands the radical substitution procedure worked well on a small scale (1–5 mmol) but was less satisfactory on a large scale. Ethyl indole-2-acetate was therefore prepared from 2-aminobenzyl alcohol by the literature method.[2]

The reduction of the 2,3-double bond of ethyl indole-2-acetate was achieved in 82% yield by using a modification of the method of reduction of indoles to indolines first described by Kikugawa.[4] He reported that

[†] This ring system is named systematically as 8,8a-dihydroazeto[1,2-*a*]indol-2(1*H*)-one and the numbering shown in **1** is that based on the systematic name.

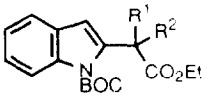
tryptophan derivatives were cleanly reduced using pyridine–borane in trifluoroacetic acid. We found that trimethylamine–borane was a better reagent for the reduction of ethyl indole-2-acetate. The dihydro ester was then hydrolysed using hydrochloric acid to 2,3-dihydroindole-2-acetic acid which was isolated (60%) as its crystalline hydrochloride. The most successful of several methods which were tried for the cyclisation of the acid to the β-lactam **1** proved to be the reaction of the acid hydrochloride with tris(2-oxo-3-benzoxazolinyl)phosphine oxide **3** and triethylamine in acetonitrile. This reagent has previously been found to be superior to other common dehydrating agents for the preparation of bicyclic β-lactams.[5] The azetidinone **1** was isolated in 37% yield as a crystalline solid.[6] The compound was purified by flash chromatography and by sublimation and it can be kept below 0 °C with little decomposition.



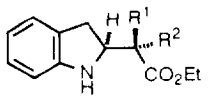
3

Methods for the introduction of substituents into the C-1 position of the azetidinone were then investigated. Ethyl indole-2-acetate was protected as its *N*-BOC derivative **4**. This could be efficiently deprotonated and methylated by successive treatment with KHMDS and iodomethane; the esters **5** (98%) and **6** (83%) were prepared in this way. These compounds were deprotected and reduced in one pot by reaction with sodium cyanoborohydride in trifluoroacetic acid, a method which has previously been used for the reduction of *N*-tosylindoles.[7] The esters **7/8** and **9** were isolated in yields of 74% and 69%, respectively. The reduction of **5** was unselective, the diastereoisomers **7** and **8** being isolated in a 1:1 ratio. This is to be expected since the reduction goes by way of an iminium cation.

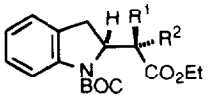
An alternative method of reduction was investigated. Compound **5** was subjected to catalytic hydrogenation over 5% rhodium on alumina at 200 psi. This gave the dihydro esters **10/11** (88%) and the reduction proved to be diastereoselective, the ratio of **10** to **11** being 5:1.[8] The stereochemistry of the major diastereoisomer **10** was established from the structure of the azetidinone **13** derived from it as described below.



4; $R^1 = R^2 = H$
5; $R^1 = Me$, $R^2 = H$
6; $R^1 = R^2 = Me$



7; $R^1 = Me$, $R^2 = H$
8; $R^1 = H$, $R^2 = Me$
9; $R^1 = R^2 = Me$



10; $R^1 = Me$, $R^2 = H$
11; $R^1 = H$, $R^2 = Me$

Molecular modelling studies were carried out on the ester **5** in an effort to understand this diastereoselectivity.[9] The minimum energy conformation **A**, and a conformation **B** which lies slightly higher in energy, are shown in the Figure. It is apparent that hydrogenation of the ester in conformation **A** is sterically less demanding than hydrogenation in conformation **B** and that hydrogen should be added preferentially from one face. This would lead to the formation of the ester **10**, which is observed to be the major diastereoisomer, since, after hydrolysis, ring closure must lead to the azetidinone **13** in which H-1 and H-8a are *cis*.

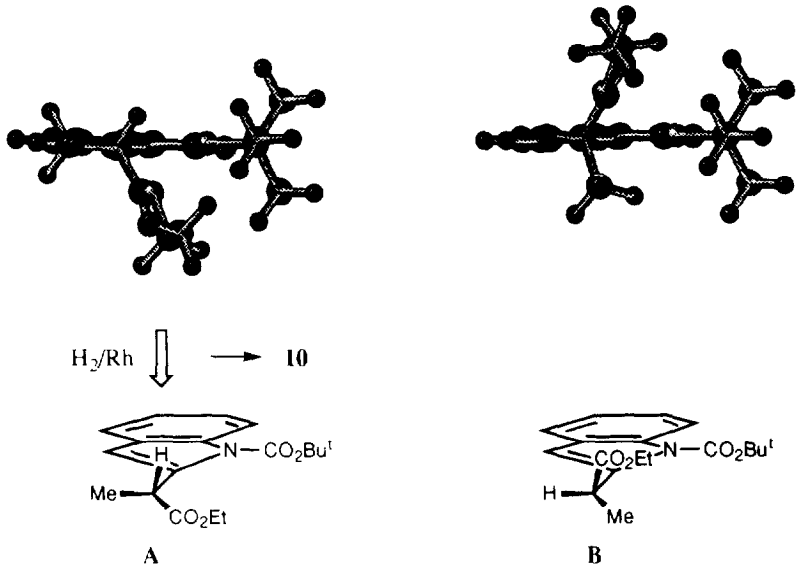
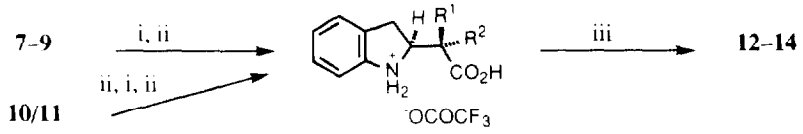


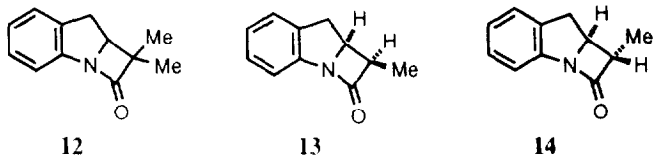
Figure Lowest energy conformation **A** and a low energy conformation **B** of ethyl *N*-BOC-indole-2-propanoate **5**. **B** is approximately 6 kJ mol^{-1} higher in energy than **A**.

The esters **7–9** were hydrolysed under basic conditions and the resulting acids were characterised as their trifluoroacetate salts. The BOC protecting groups were removed from the esters **10** and **11** (using TFA) and the products were then similarly hydrolysed. The carboxylic acid salts were then cyclised as before to give the corresponding azetidinones (Scheme 2). The azetidinone **12** was isolated as a stable crystalline solid[10] in an overall yield of 73% from the ester **9**. The mixture of esters **7** and **8** gave, in 56% overall yield, a crystalline 1:1 mixture of the azetidinones **13** and **14** and the esters **10** and **11** gave (62%) a 5:1 mixture of the same azetidinones.[11] The structures of compounds **13** and **14** were determined from their ^1H NMR spectra; in particular, from the H-1 to H-8a coupling constants (J = 5.5 Hz for **13**, 2.8 Hz for **14**).



i, KOH, EtOH–H_2O; ii, CF_3CO_2H; iii, 3, NEt_3, MeCN, 80 °C, 6 h.

Scheme 2

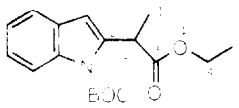


12 **13** **14**

The development of these methods for synthesising the ring system should allow more highly functionalised derivatives to be prepared.

Acknowledgements: We thank Dr M. J. Pearson for discussion and SmithKline Beecham Pharmaceuticals for support. We also thank the EPSRC for a CASE Studentship (to K. G.).

1 Joyeau, R.; Yadav, L.D.S.; Wakselman, M. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1899–1907.
2 Capuano, L.; Ahlheim, A.; Hartmann, H. *Chem. Ber.*, **1986**, *119*, 2069–2074.
3 Baciocchi, E.; Muraglia, E.; Sleiter, G. *J. Org. Chem.*, **1992**, *57*, 6817–6820.
4 Kikugawa, Y; *J. Chem. Res. (S)*, **1978**, 184–185.
5 Nagamatsu, T.; Kunieda, T. *Chem. Pharm. Bull.*, **1988**, *36*, 1249–1251.
6 This and other new compounds have been fully characterised. For **1**, m.p. 77 °C; ν_{max} (nujol) 1773 cm^{-1}; δ (200 MHz, $CDCl_3$) 2.98 (1 H, dd, *J* 16.4 and 3.0 Hz, H-1 *endo*), 3.15 (1 H, dd, *J* 16.8 and 7.8 Hz, H-8 *endo*), 3.37 (1 H, dd, *J* 16.8 and 8.8 Hz, H-8 *exo*), 3.53 (1 H, dd, *J* 16.4 and 5.2 Hz, H-1 *exo*), 4.20–4.50 (1 H, m, H-8a) and 7.00–7.25 (4 H, m, Ar-H); *m/z* 159 (M^+, 33%) and 117(100).
7 Ketcha, D.M.; Lieurance, B.A. *Tetrahedron Lett.*, **1989**, *30*, 6833–6866.
8 The diastereoselectivity of this reduction is consistent with that which we have observed in several hydrogenations of related compounds.
9 After building and geometry optimisation using the molecular mechanics within SYBYL[12] the molecule **5** was submitted for full geometry optimisation using the AM1 method in MOPAC.[13] The following conformational searches were then performed using the Tripos force field within SYBYL:
(i) a random conformational search around 9 bonds, with 1000 conformations considered and using Gasteiger–Hückel charges.
(ii) a gridsearch, rotating C_2–C_2 through 360° in 15° intervals, without charges;
(iii) as in (ii) and using Gasteiger–Hückel charges.
(iv) a gridsearch with Gasteiger–Hückel charges rotating bonds C_2–$C_{2'}$, $C_{2'}$–$C_{3'}$, $C_{3'}$–$O_{4'}$ and $O_{4'}$–$C_{5'}$ through 360° in 60° intervals.
In all searches the minimum energy conformation was similar to that depicted in **A** in the Figure, with the methyl group eclipsing the plane of the indole ring.



10 Compound **12**, m.p. 82–83 °C; ν_{max} (nujol) 1777 cm^{-1}; δ (200 MHz, $CDCl_3$) 1.24 (3 H, s, Me-1 *endo*), 1.52 (3 H, s, Me-1 *exo*) 3.05–3.29 (2 H, m, H-8), 4.17 (1 H, dd, *J* 9.3 and 8.3 Hz, H-8a) and 7.02–7.27 (4 H, m, Ar-H); *m/z* 187 (M^+, 59%) and 144(100).
11 The mixtures of **13** and **14** were low melting crystalline solids (1:1, m.p. 35–40 °C; 5:1, m.p. 40–68 °C) which gave correct C, H and N analyses; ν_{max} (nujol) 1771 cm^{-1}; δ (200 MHz, $CDCl_3$) 1.25 (d, *J* 7.7 Hz, Me-1 of **13**), 1.48 (d, *J* 7.7 Hz, Me-1 of **14**), 3.05–3.40 (m, H-8 of **13**, H-8 of **14** and H-1 of **14**), 3.70 (qd, *J* 7.7 and 5.5 Hz, H-1 of **13**), 4.46 (ddd, *J* 8.8, 7.7 and 2.8 Hz, H-8a of **14**), 4.17 (1 H, ddd, *J* 9.4, 8.2 and 5.5 Hz, H-8a of **13**) and 7.01–7.25 (Ar-H); *m/z* 173 (M^+, 27%) and 117(100).
12 SYBYL is a Trademark of TRIPOS, Inc., St. Louis, MO, U.S.A.
13 Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.*, **1985**, *107*, 3902–3909.

(*Received in UK* 8 *September* 1995; *accepted* 22 *September* 1995)