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Formation of a Medium Ring Imino Ether by a Diazo Insertion Reaction

Ronald H. B. Galt,[a] Peter B. Hitchcock,[b] Sean J. McCarthy[b] and Douglas W. Young[b]*

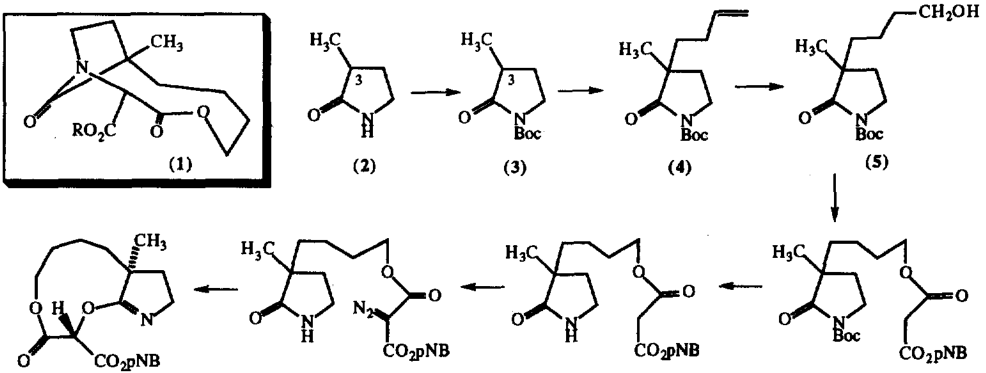
[a]Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, SK10 4TG

[b]School of Chemistry and Molecular Sciences, University of Sussex, Falmer, Brighton, BN1 9QJ, U.K.

Abstract : Intramolecular carbene insertion, designed to prepare an anti-Bredt amide by insertion into an amide NH bond has proceeded by attack at the amide oxygen to yield the fused bicyclic imino ether **(9)** with complete diastereoselectivity. Copyright © 1996 Elsevier Science Ltd

As part of a programme to prepare anti-Bredt amides which contain a carboxyl group on the carbon atom attached to the amide nitrogen and which therefore have potential to target penicillin binding proteins (PBPs),[1] we decided to synthesise the bicyclo[2.1.7] compound **(1, R = H)**. In the course of these studies, we have discovered a novel mode of carbene insertion into an amide.

Commercially available 3-methyl-2-pyrrolidinone **(2)** was chosen as starting material for our synthesis and was activated at C-3 by conversion to the urethane **(3)**† in 96% yield using $(Boc)_2O$ and DMAP in CH_3CN as shown in Scheme 1. Treatment of the amide-urethane **(3)** with LHMDS in THF containing one equivalent of HMPA at -78 °C, followed by reaction with 5-bromopent-1-ene gave the olefin **(4)**† as an oil in 63% yield. This was reacted with BH_3.THF in THF, followed by alkaline H_2O_2 to give the alcohol **(5)**† as an oil in variable yields of 35 - 75%. Reaction of the alcohol **(5)** with *para*-nitrobenzyl malonyl chloride in CH_2Cl_2 containing pyridine gave the diester **(6)**† which, on treatment with CF_3CO_2H in CH_2Cl_2, yielded the amido ester **(7)**†. A diazo function was now introduced into the molecule by reaction with carboxybenzenesulfonyl azide in CH_3CN at 0 °C and the resultant crude diazo-compound **(8)** was heated to reflux in benzene containing a small amount of rhodium octanoate, to yield a solid, m.pt. 94 - 96 °C, in an overall yield of 37% from the ester **(7)**.



Scheme 1

The empirical formula and the ^1H-NMR spectrum of the product were in keeping with its assignment as the desired bicyclic amide **(1, R = pNB)**, although there was no observable long range coupling in the CH proton between the two carbonyl groups, nor did the compound exhibit nOe to any other protons in the molecule. The well known difficulty in spectroscopically distinguishing between imino ethers and lactams[2] was resolved by the ^{15}N-NMR spectrum which showed an absorption for the aromatic nitro group at δ -16.8 ppm and for an sp^2

hybridised nitrogen at δ -140.3 ppm. This is more in keeping with the structure (**9**) where diazo insertion at the amide has yielded an imino ether. To confirm the structure, the compound was subjected to X-ray crystallographic analysis,[3] the result of which is shown in Figure 1. This indicates that the insertion reaction has yielded the imino ether (**9**) as a single diastereoisomer in which the bridgehead methyl group is *trans* to the hydrogen at the newly created asymmetric centre.

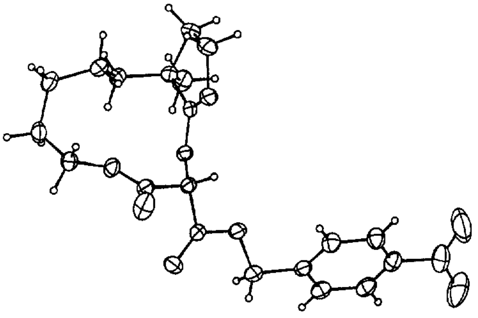
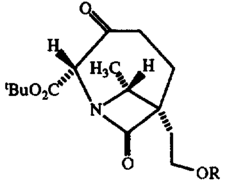
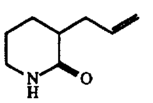


Figure 1 : Structure of the imino ether (9), determined by single crystal X-ray diffraction

Although carbenes are known[4] to insert into the oxygen atom of ketone, ester and tertiary amide groups to yield ylides which can be trapped, insertion of a carbene into a secondary amide usually proceeds with C-N bond formation.[5] The one example of carbene - NH insertion to yield a bicyclic system is in the synthesis of the amide (**10**),[1(c)(d)] where it may be argued that the β-lactam NH in the precursor has more amine character than our lactam (**8**). There are examples of formation of imino ethers in radical cyclisation reactions on amides and, although reaction of the amide (**11**) with benzeneselenyl chloride was at first thought to yield the diastereoisomeric bicyclic lactams (**12**),[6] the structures of the products later had to be revised to those of the imino ethers (**13**).[7]



(10)



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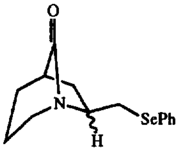

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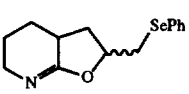

(13)

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References and Notes

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2. Hernández, R.; Medina, M. C.; Salazar, J. A.; Suárez; E., Prangé, T., *Tetrahedron Lett.*, **1987**, *28*, 2533 - 2536.
3. **Crystal data:** $C_{20}H_{24}N_2O_7$, M = 404.4, monoclinic, space group $P2_1/c$ (No. 14), a = 11.916 (4), b = 8.420 (2), c = 20.259 (4) Å, β = 105.05 (2)°, U = 1962.9 (9) Å^3, Z = 4, D_c = 1.37 mg m^{-3}, F (000) = 856. Monochromated Mo-Kα X-rays, λ = 0.71073 Å, μ = 0.10 mm^{-1}, crystal size 0.4 x 0.4 x 0.4 mm^3. Refinement on F^2 using SHELXL-93 and 4720 unique reflections gave R1 = 0.050 (for 3390 reflections with $I > 2\sigma(I)$) and wR2 = 0.141 (for all reflections). Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC).
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† These compounds had the expected analytical and spectroscopic data.

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