Simple azetidine *N*-oxides: synthesis, structure and reactivity

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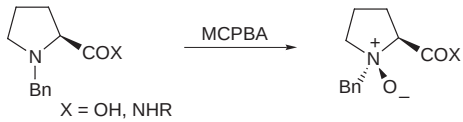
The preparation of two stable azetidine *N*-oxides is described; one structure was confirmed by X-ray crystallography and the second was found to undergo a quantitative ring expansion to yield a new 6-hydroxy tetrahydro-1,2-oxazine, a potentially useful reagent for further synthetic transformations.

Azetidine *N*-oxides are usually unstable at room temperature, undergoing a [1,2] rearrangement.[1] Only one example of an azetidine *N*-oxide stable at room temperature has been reported.[2] In this case the azetidine ring was fused to a six membered ring. Related compounds include azetidine aminoxyls and nitrones.[3]

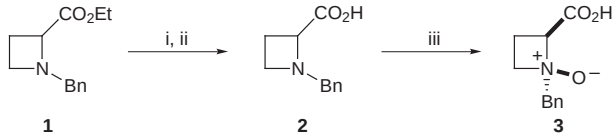
Recent work has shown that tertiary amine oxides derived from proline and pipecolic acid derivatives are stabilised by intramolecular hydrogen bonding if a suitable hydrogen bonding donor group is present in the carboxylic acid side chain. The amine oxides are formed as single diastereoisomers where the amine oxide is *syn* to the carboxylic acid side chain (Scheme 1).[4]



Scheme 1

We were intrigued by the possibility of synthesising the corresponding *N*-benzyl-2-carbonylazetidine *N*-oxides in order to establish if they would be stablised by intramolecular hydrogen bonding. In addition, such compounds should possess novel and useful synthetic potential as a consequence of ring strain.

Racemic ethyl *N*-benzylazetidine-2-carboxylate **1** was prepared according to route of Wasserman.[5] Saponification of the ester with $Ba(OH)_2$ followed by acidification gave the free acid **2**. Oxidation with MCPBA furnished the desired azetidine *N*-oxide **3** in 30% yield as a stable compound (Scheme 2). In contrast, all attempts to form the *N*-oxide of ester **1** led to complex mixtures of products and none of the desired material was ever isolated.



Scheme 2 *Reagents and conditions*: i, $Ba(OH)_2$; ii, H_3O^+; iii, MCPBA, 30% over 3 steps

From spectroscopic data the *N*-oxide **3** had clearly been formed as a single diastereoisomer. Crystals of suitable quality for X-ray analysis were grown and the X-ray structure clearly showed that the amine oxide had been formed *syn* to the carboxylic acid and that there was an intramolecular hydrogen bond between the amine oxide oxygen and the carboxylic acid (Fig. 1). To the best of our knowledge this is the first example of a simple, stable azetidine *N*-oxide characterised by X-ray crystallography.[6]

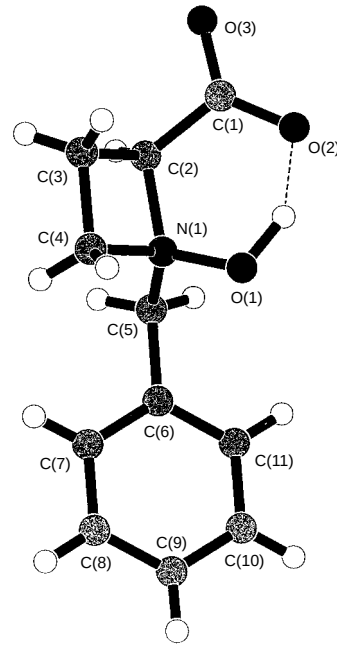
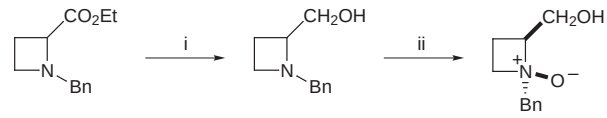


Fig. 1 Crystal structure of **3**

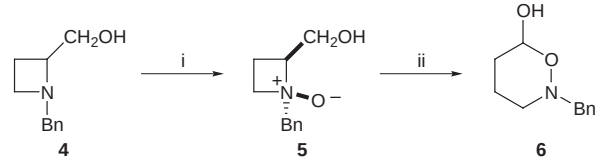
In order to establish if other hydrogen bond donor groups could stabilise azetidine *N*-oxides, the ester **1** was reduced to the primary alcohol **4** with $LiAlH_4$. Oxidation with MCPBA yielded the amine oxide **5** as a single diastereoisomer, in a much higher yield of 63% (Scheme 3). Again this compound was stable at room temperature and full spectroscopic data were obtained.



Scheme 3 *Reagents and conditions*: i, $LiAlH_4$, THF, −78 °C to room temp., 90%; ii, MCPBA, 63%

Upon attempted recrystallisation from hot CH_2Cl_2, the amine oxide underwent a quanitative conversion to a new less polar material (Scheme 4).

The presence of a signal at δ 5.2 in the ^{1}H NMR spectrum suggested that oxazine **6** had been formed. We can rationalise this conversion either as a Cope-type elimination followed by tautomerism of the enol to an aldehyde and lactol formation, or as a [1,2] rearrangement. Such rearrangements have precedent,



Scheme 4 *Reagents and conditions*: i, MCPBA, 63%; ii, CH_2Cl_2, reflux, quant.

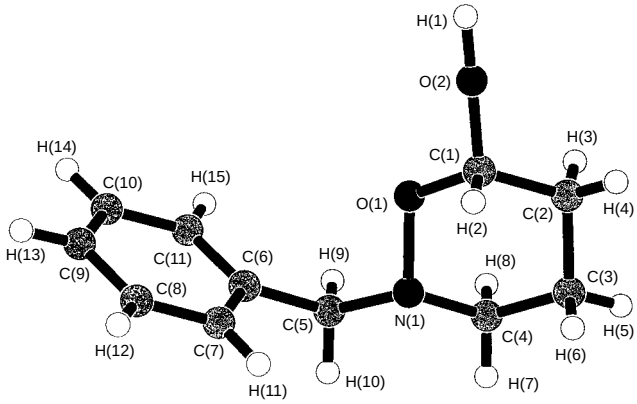
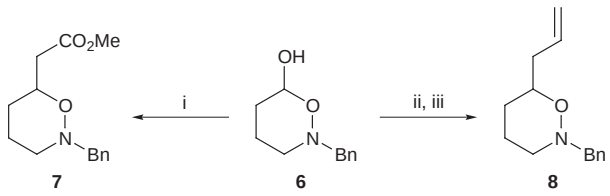


Fig. 2 Crystal structure of **6**

exemplified by the conversion of physostigimine *N*-oxide to geneserine.[7] The structure of tetrahydrooxazine **6** was confirmed by single crystal X-ray analysis of the product (Fig. 2).[6]

This 6-hydroxytetrahydrooxazine in which the nitrogen bears a benzyl group has not been previously prepared. Interestingly, the crystal structure shows that the anomeric hydroxy group is in an equatorial position. We have carried out some preliminary studies on the chemistry of this ring system and have established that it undergoes reactions typical of a lactol. For example, treatment of tetrahydrooxazine **6** with the stabilised ylide shown gave the ester **7** *via* initial alkene formation followed by an intramolecular Michael addition.[8] Conversion of the tetrahydrooxazine **6** to its acetate followed by reaction with allyltrimethylsilane in the presence of BF_3–OEt_2 yielded the allyl adduct **8** (Scheme 5).



7 **6** **8**

Scheme 5 *Reagents and conditions*: i, Ph_3P = $CHCO_2Me$, THF, 68%; ii, AcCl, NEt_3, CH_2Cl_2; iii, $AllylSiMe_3$, $BF_3{\cdot}OEt_2$, 30% over 2 steps

In summary, we have prepared and characterised the first stable simple azetidine *N*-oxide **3** and shown that it is stabilised by intramolecular hydrogen bonding to the carboxylic acid. The corresponding *N*-benzyl-2-hydroxymethylazetidine *N*-oxide **5** undergoes rearrangement in warm CH_2Cl_2 to give a novel tetrahydrooxazine **6**, which shows coupling reactions typical of a lactol.

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Notes and References

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6 *Crystal data* for **3** (from CH_2Cl_2): $C_{11}H_{13}NO_3$, M = 207.23, orthorhombic, space group *Pbca*, Z = 8, a = 10.998(3), b = 16.750(4), c = 10.837 Å, U = 1996.3(10) Å^3, D_c = 1.379 g cm^{-3}; T = 153 K; max 2θ = 49.9°, graphite-monochromated Mo-Kα radiation (λ = 0.71069Å), 2020 reflections were measured; of these, 1277 with $F > 0.30\sigma(F)$ were used in the refinement; R = 0.077, R_w = 0.081, residual electron density 0.44/−0.48 e Å^{-3}. For **6** (from CH_2Cl_2): $C_{11}H_{15}NO_2$, M = 193.24, monoclinic, space group $P2_1/c$ (no 14), Z = 4, a = 9.036(6), b = 13.551(6), c = 8.478(4) Å, β = 99.70(4), U = 1023.4(9) Å^3, D_c = 1.254 g cm^{-3}; T = 153 K; max 2θ = 50.0°, graphite-monochromated Mo-Kα radiation (λ = 0.71069Å), 2008 reflections were measured; of these, 1877 were unique with 1325 $F > 1.00\sigma(F)$ used in the refinement; R = 0.052, R_w = 0.040, residual electron density 0.81/−0.96 e Å^{-3}. CCDC 182/893.

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