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The Highly Stereoselective Formation of Pipecolic Acid *N*-Oxide and Related Derivatives

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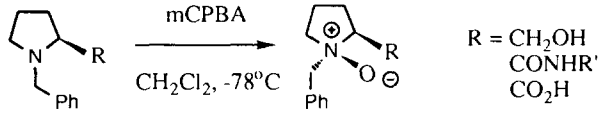
Abstract: *N*-Alkylated derivatives of pipecolic acid are shown to undergo highly stereoselective oxidation to give stable tertiary amine *N*-oxides. The ester derivatives show a high degree of stability compared to their proline analogues. © 1997 Elsevier Science Ltd.

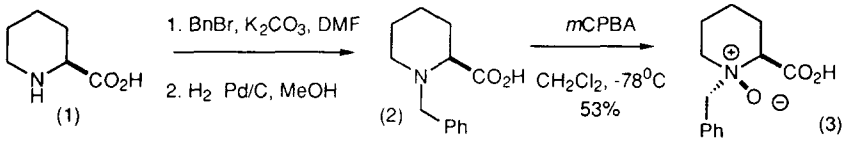
We have recently reported the preparation of several novel amine oxides derived from the amino acid proline. In compounds which bear a hydrogen bond donor in the carboxylic acid side chain (such as acid, alcohol or amide) the *N*-oxide is formed *syn* to the hydrogen bond donor and is stabilised by intramolecular hydrogen bonding[1]. Examples are given in scheme 1.

Scheme 1.



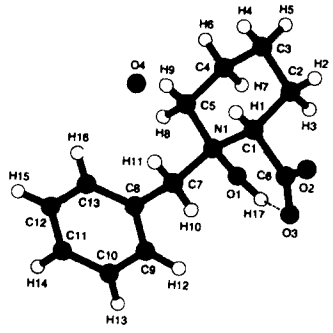
We have also shown that certain derivatives of these *N*-oxides function as catalysts in the borane mediated reduction of ketones, which in certain cases, gave alcohols with good enantioselectivity[2]. The success of these studies prompted us to investigate the formation of the corresponding six membered ring analogues. In particular, we anticipated that the six membered ring compounds should have a more rigidly defined conformation and this was of particular interest with regard to our studies on *N*-oxides as control elements in the synthesis of conformationally defined oligomers, peptidiomimetics and chiral catalysts. Thus, we initially examined the oxidation of racemic *N*-benzyl pipecolic acid[3] (Scheme 2).

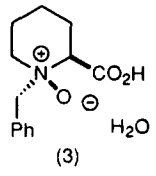
Scheme 2.



The *N*-oxide (3) was formed as a single stereoisomer by oxidation of the tertiary amine (2) with *m*CPBA. It was isolated as a solid which crystallised on standing open to the atmosphere. The X-ray structure of the *N*-oxide (3) showed it had formed with the *N*-oxide oxygen *syn* to the carboxylic acid side chain with an intramolecular hydrogen bond present (Figure 1)[4]. The *N*-oxide clearly adopts an axial orientation with regard to the six membered ring[5]. The *N*-oxide also possesses a molecule of water of crystallisation, this is in complete contrast to the *N*-benzylproline *N*-oxide which is non-hydrated even on standing open to the atmosphere.

Figure 1.

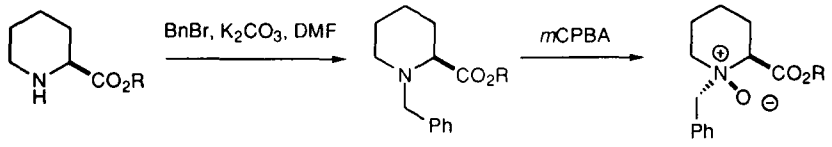




(3)

The corresponding ester *N*-oxides were then prepared to evaluate the selectivity in their formation and stability. The precursor tertiary amines were prepared by alkylation of the corresponding secondary amines, followed by oxidation with *m*CPBA (Scheme 3).

Scheme 3.



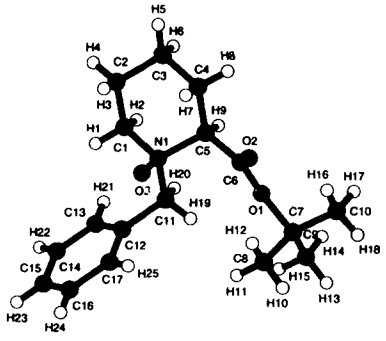
The results are summarised in table 1.

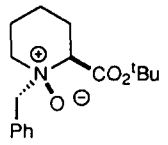
Table 1.

Entry	Ester	% Yield *N*-Oxide	*cis:trans*
1	Me	40	8.5 : 1
2	Et	48	6.5 : 1
3	^{t}Bu	52	25 : 1

The ester *N*-oxides were formed as *cis/trans* mixtures with the *cis* isomer predominating in each case. The highly selectivity in the formation of the *tert*-butyl ester *N*-oxide is noteworthy. A single recrystallisation gave the pure *syn* stereoisomer. What was suprising was the high degree of stability of these compounds. They could be stored on the bench at room temperature with only a modest degree of decomposition. This is in complete contrast to the proline ester *N*-oxides which decomposed quickly at room temperature. The relative configuration of the major stereoisomer of the *tert*-butyl ester *N*-oxide was confirmed by X-ray analysis (Figure 2). This again showed the axial orientation of the *N*-oxide oxygen. Interestingly no water of crystallisation could be detected either by X-ray or by spectroscopic methods.

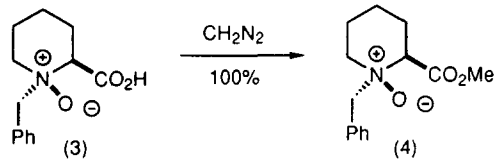
Figure 2.





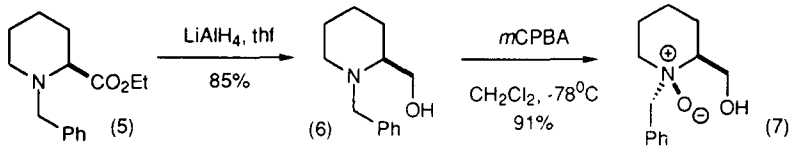
This stability prompted us to prepare a pure sample of the methyl ester *syn* *N*-oxide by methylation of the acid *N*-oxide. Thus treatment of acid (3) with excess diazomethane (10 eqs) gave the methyl ester in quantitative yield (Scheme 4). Again, the pure *syn* *N*-oxide decomposed only slowly on standing at room temperature.

Scheme 4.



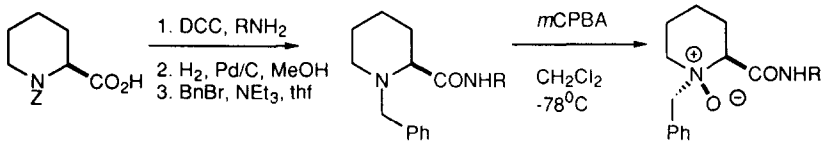
The oxidation of the hydroxymethyl compound (6) was examined. Reduction of the ethyl ester (5) with $LiAlH_4$ yielded the requisite alcohol (6), which underwent oxidation to give a single diastereoisomeric *N*-oxide (7) in 91% yield (Scheme 5).

Scheme 5.



We also examined the oxidation of several *N*-benzyl pipecolic acid amide derivatives. These were prepared by the route shown in scheme 6.

Scheme 6.



Oxidation of the tertiary amines gave the amine oxide amides as a single *syn* stereoisomer in each case. The presence of intramolecular hydrogen bonding between the N-oxide oxygen and the amide NH was indicated by the downfield shift of the NH signal in the ^{1}H-NMR. The results are summarised in table 2.

Table 2.

Entry	R	% Yield *N*-Oxide	δ, NH (ppm)
1	Me	98	10.19
2	Et	86	10.36
3	^{t}Bu	96	10.58

In summary, we have shown that *N*-benzylated pipecolic acid derivatives undergo a highly diastereoselective oxidation to yield the corresponding tertiary amine *N*-oxides. In particular, the ester derivatives exhibit a high degree of stability compared to their proline analogues. X-ray analysis clearly shows the high preference for the *N*-oxide to adopt an axial orientation in the six membered ring systems. We are currently exploring the use of these stable *N*-oxides in a number of diastereoselective transformations.

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2. O'Neil, I. A.; Turner, C. D.; Kalindjian, S. B. *Synlett*, **1997**, 777.
3. Racemic pipecolic acid was used in this study; all compounds described are racemic. Relative stereochemistry is shown in all diagrams.
4. We thank J. V. Barkley for this structure determination. Full crystallographic data will be deposited at the Cambridge Crystallographic Database.
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