Enantioselective Synthesis of Oxazolidinones from *N*,*N*-Dibenzylamino Epoxides

Gabriel E. Vargas, María M. Afonso, J. Antonio Palenzuela*

Instituto Universitario de Bio-Orgánica 'Antonio González', Departamento de Química Orgánica, Universidad de La Laguna, 38206 La Laguna, Tenerife, Spain
Fax +34(922)318442; E-mail: jpalenz@ull.es

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Abstract: Enantiomerically pure oxazolidinones are easily prepared from *N*,*N*-dibenzylamino epoxides through a one-pot procedure involving monodeprotection of the amino group and treatment with $NaHCO_3$.

Key words: amino epoxides, cyclization, oxazolidinones, heterocycles

The oxazolidinones are a group of heterocycles which have been subjected to numerous studies due to their biological properties,[1] they also serve as efficient chiral auxiliaries[2] and are useful synthetic intermediates in the preparation of other important compounds, especially amino alcohols.[3]

The strategies devised for the synthesis of oxazolidinones are quite varied; the most common being the treatment of amino alcohols with phosgene or the intramolecular cyclization of hydroxy carbamates.[4]

Recently, Génisson and co-workers presented the synthesis of oxazolidinones from *N*-benzylamino epoxides by treatment with ammonium carbonate through a one-pot carboxylation–cyclization sequence.[5] According to the authors, and based on the work of Toda and co-workers,[6] the reaction takes place by the attack of the monoprotected amino group onto the carbon dioxide produced by the carbonate followed by the regioselective intramolecular opening of the epoxide by the thus formed carbamate, the reaction being catalyzed by the ammonium ion.

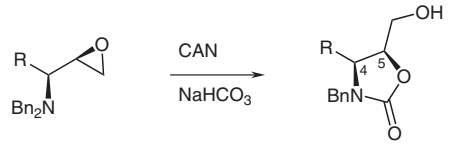
Later, Nagase and co-workers[7] presented a three-component synthesis which involved an amine, a haloepoxide, and a metal carbonate, proposing that the mechanism proceeds through the attack of the amine on the haloepoxide to give an intermediate amino epoxide. Attack of the carbonate on the epoxide followed by an intramolecular cyclization gives a six-membered cyclic carbamate which then rearranges to the oxazolidinone.

Thus it seems clear that the treatment of amino epoxides with a carbonate salt is an excellent route towards the oxazolidinone moiety, although the mechanism of formation can be different depending on the reaction conditions.

Enantiomerically pure *N*,*N*-dibenzylamino epoxides are easily obtained from amino acids following the procedure of Barluenga and co-workers,[8] and we envisaged that coupling a monodeprotection procedure with the treatment with a carbonate salt could lead to a simple synthesis of oxazolidinones.

The deprotection of an *N*-benzyl group can be effected by a number of methods, however, selectivity for mono- or di-N-debenzylation is difficult to achieve,[9] and very few procedures exist to remove only one benzyl group of an *N*,*N*-dibenzylamine.[10] The procedure of Grayson and Davis using *N*-iodosuccinimide[10a] did not work well in our case; whereas the one published by Davies and co-workers using cerium ammonium nitrate (CAN) in acetonitrile[10b] gave a clean reaction with only one major product as judged by TLC.

In this case the ammonium ion could help with the opening of the epoxide as suggested by Génisson[5] and the treatment of the crude product with a carbonate salt should result in the desired oxazolidinone. After several trials we found that the addition of the salt was not necessary, since the published protocol called for vigorous stirring with sodium bicarbonate, which was enough to produce the carboxylation of the monodeprotected amino alcohol and the subsequent intramolecular cyclization.



1 R = Me
2 R = *i*-Bu
3 R = Bn

4 R = Me (85%)
5 R = *i*-Bu (81%)
6 R = Bn (80%)

Scheme 1

Thus, the treatment of **1** with CAN in acetonitrile–water, followed by the addition of an aqueous saturated solution of $NaHCO_3$ and vigorous stirring, furnished the oxazolidinone **4** in high yield (85%) and with total selectivity (Scheme 1).[11] The structure of the new compounds was established by a combination of spectroscopic analyses.[12] Regarding the stereochemistry of the ring, the value of the coupling constant between H-4 and H-5 (8.3 Hz) clearly indicates a *cis*-substituted system.[13]

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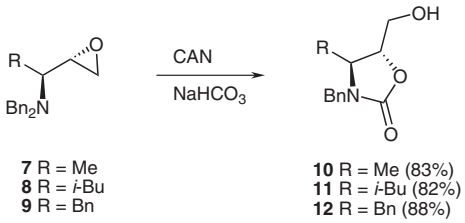
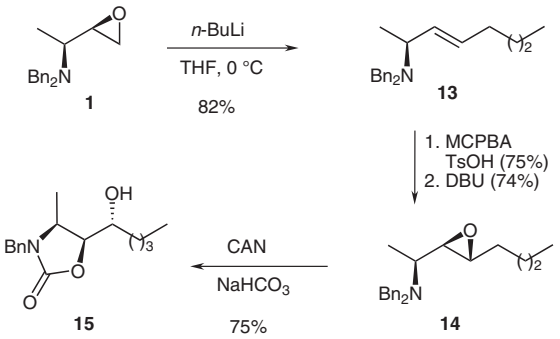
The reaction also worked well when the amino epoxides derived from other amino acids, such as **2** and **3** were subjected to the same reaction conditions as shown in Scheme 1, yielding the oxazolidinones **5** and **6** in good yields as a single isomer in each case.

Diastereomeric epoxides **7**–**9**, prepared following Barluenga's procedure from **1**–**3**,[8] were also tested and the corresponding oxazolidinones **10**–**12** isolated (Scheme 2). The value of the coupling constant between H-4 and H-5 (<5.5 Hz in all cases) allowed us to establish that the *trans*-oxazolidinones were formed, indicating a total selectivity in this process.



Scheme 2

To extend the scope of the reaction, a disubstituted amino epoxide was prepared by first transforming **1** into the allylamine **13** with *n*-butyllithium.[14] Compound **13** was then subjected to the epoxidation conditions for amino alkene compounds[15] giving **14** in 82% yield. The treatment of **14** with CAN followed by vigorous stirring with $NaHCO_3$ gave the oxazolidinone **15** in good yield, again as a single isomer (Scheme 3).

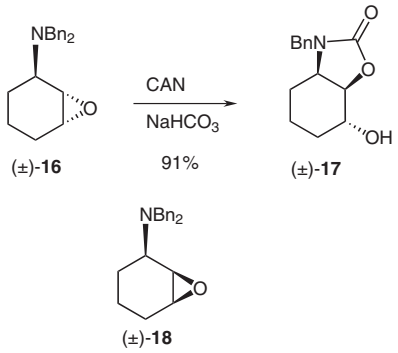


Scheme 3

The relative stereochemistry of the oxazolidinone ring in **15** was assigned as *cis* on the basis of the value of the H-4–H-5 coupling constant (6.8 Hz) but the relative stereochemistry of the hydroxyl group was more difficult to establish, and so it was deduced from the analysis of the coupling constants of the relevant protons. Comparing the experimental values with the computed ones[16] for all possible isomers allowed us to establish the stereochemistry of **15** as shown in Scheme 3.

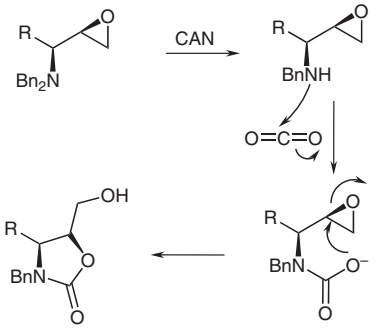
To study the stereoelectronic requirements of the reaction, the cyclic *N*,*N*-dibenzylamino epoxides **16** and **18** were prepared in racemic form,[15] and were subjected to the reaction conditions for the formation of oxazolidinones. The *anti*-amino epoxide **16** gave the expected oxazolidinone **17** as a single compound in a 91% yield (Scheme 4). The *syn*-amino epoxide **18** in contrast showed poor reactivity, giving a complex mixture in low yield from which no oxazolidinone could be isolated.

These results indicate that the groups involved in the reaction, the epoxide and the intermediate carbamate, need to adopt a precise relative disposition for the success of the process.



Scheme 4

The structure and relative stereochemistry of the oxazolidinones obtained in this work indicate that the mechanism operating here is the one postulated in the works of Toda[6] and Genisson;[5] that is, the attack of the nitrogen onto the CO_2 liberated by the carbonate salt and the intramolecular cyclization of the intermediate formed. This results in the inversion of configuration at the carbon atom of the epoxide closer to the nitrogen and in the retention at the other epoxide carbon (Scheme 5).



Scheme 5

The simple, one-pot procedure outlined in this communication permits the easy preparation of enantiomerically pure oxazolidinones with different degrees of substitution from amino epoxides, which in turn can be efficiently prepared from commercial amino acids.

Acknowledgment

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(11) **General Experimental Procedure for the Preparation of Oxazolidinones from *N*,*N*-Dibenzyl Amino Epoxides**
To a 0.05 M solution of the amino epoxide in MeCN–H_2O (5:1) was added CAN (2.1 equiv) and the reaction was stirred at r.t., following the progress by TLC (approx. 12 h). Then a sat. aq soln of $NaHCO_3$ was added, and the mixture was vigorously stirred for 10 min. After extraction with Et_2O, drying over Na_2SO_4 and concentration, the crude reaction mixture was purified by chromatography to give the pure oxazolidinone.

(12) **Representative Data**
Oxazolidinone **4**: $[\alpha]_D^{20}$ –67.9 (*c* 1.2, $CHCl_3$). IR: ν_{max} = 3415, 2927, 1731, 1424, 1052 cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ = 7.27 (m, 5 H), 4.75 (d, *J* = 15.3 Hz, 1 H), 3.91 (dt, *J* = 5.0, 8.3 Hz, 1 H), 3.80 (d, *J* = 15.3 Hz, 1 H), 3.37 (d, *J* = 5.0 Hz, 2 H), 3.16 (dq, *J* = 6.6, 8.3 Hz, 1 H), 0.68 (d, *J* = 6.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7 (s), 135.7 (s), 128.8 (d), 128.0 (d), 127.9 (d), 76.7 (d), 60.8 (t), 51.8 (d), 45.6 (t), 12.5 (c). LRMS (EI): *m/z* (%) = 221 (29)[M^+], 91 (100). HRMS (EI): *m/z* calcd for $C_{12}H_{15}NO_3$: 221.1052; found: 221.1043.

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(16) Each possible isomer was subjected to a conformational search using Molecular Mechanics (PCMODEL v7, Serena Software, Bloomington, IN). The coupling constants in each conformer were calculated and the Boltzmann weighted average was used for the comparison with the experimental values.

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