

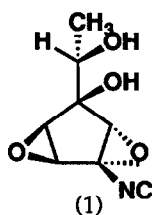
## The Preparation of Epoxy Isonitriles (Isocyanooxiranes)

J.E.Baldwin\* and I.A.O'Neil<sup>1</sup>

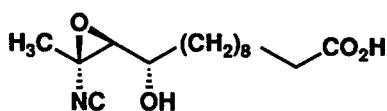
Dyson Perrins Laboratory and the Oxford Centre for Molecular Sciences,  
South Parks Rd, Oxford OX1 3QY. U.K.

**Summary:** The preparation of epoxy isonitriles from vinyl formamides using an epoxidation / dehydration sequence is described.

As part of our effort towards the total synthesis of the isonitrile containing metabolites isonitrin A,B and C<sup>2</sup>, we needed to develop a practical synthesis of epoxy isonitriles<sup>3</sup>, a hitherto inaccessible functionality found in isonitrin C (trichoviridin) (1) and aerocyanidin (2) a more recently reported natural product<sup>4</sup>.



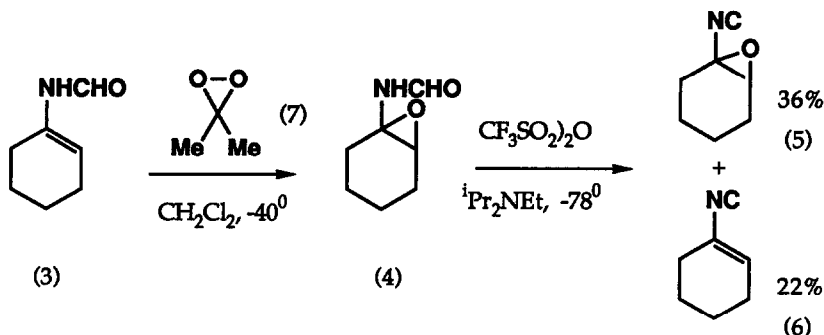
(1)  
Isonitrin C  
Trichoviridin



(2)  
Aerocyanidin

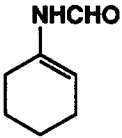
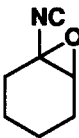
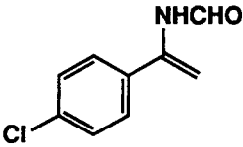
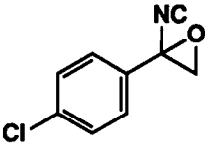
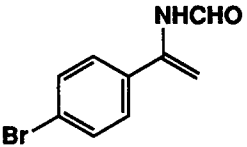
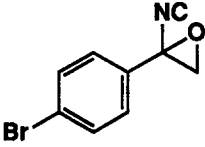
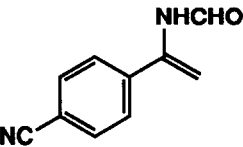
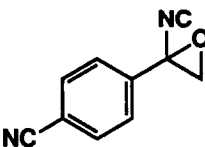
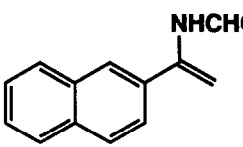
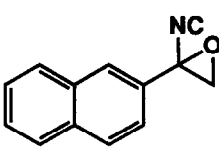
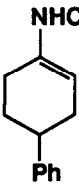
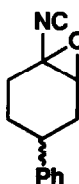
We had previously attempted to prepare epoxy isonitriles by the direct epoxidation of vinyl isonitriles<sup>5</sup>, however this route failed to give any of the desired product. This is not altogether surprising in view of the ease of oxidation of an isonitrile group<sup>6</sup> coupled with its electron withdrawing ability which deactivates the double bond towards attack by electrophilic epoxidizing reagents. In view of the above we chose to investigate the route shown in scheme 1 involving the epoxidation of a vinyl formamide to give an intermediate epoxy formamide which would be dehydrated to yield the required epoxy isonitrile.

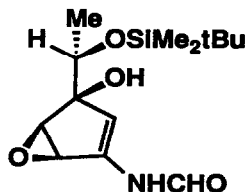
## Scheme 1



It was anticipated that the intermediate epoxy formamide (4) would be highly reactive particularly in the presence of acid<sup>7</sup>. We therefore decided to employ an epoxidizing reagent which was as neutral as possible and produced non acidic by products. We chose to use dimethyldioxirane<sup>8</sup> (7). Treatment of cyclohexene formamide (3) with one equivalent of dimethyldioxirane (7) at  $-40^\circ$ , followed by addition of diisopropylethylamine (Hunig's base) (3eq.) and trifluoromethanesulphonic (triflic) anhydride (1.2eq.) at  $-78^\circ$  gave a mixture of the epoxy isonitrile (5) and cyclohexene isonitrile (6) the latter arising presumably from dehydration of unreacted starting material. The two products were separated by flash chromatography on silica. Both were volatile, foul smelling oils, although the odour of the epoxy isonitrile (5) was perceptibly different from the vinyl isonitrile (6). This procedure appears to be quite general and we have prepared a variety of epoxy isonitriles using this methodology (table 1). There are several important points concerning the experimental procedure in this methodology. Firstly, we prepared the dimethyldioxirane according to the procedure of Eaton and Wicks<sup>9</sup>. Thorough drying of the reagent with activated 4A molecular sieves was essential to avoid hydrolysis of the triflic anhydride. We found that the use of magnesium sulphate led to decomposition of the dioxirane in agreement with the recent report of Danishefsky<sup>10</sup>. Secondly, addition of excess dioxirane gave decreased yields of the products, presumably because the epoxy isonitrile is susceptible to oxidation giving an epoxy isocyanate which decomposes. Thirdly, the use of triflic anhydride/Hunig's base for the dehydration of the intermediate epoxy formamide is essential to the success of the reaction<sup>11</sup>. We have investigated the use of phosgene based reagents<sup>12</sup> in this step and they failed to give any of the desired product.

We have recently completed a total synthesis of isonitrin B (deoxytrichoviridin)<sup>2</sup> which involves the dehydration of the vinyl formamide (8). This methodology could potentially allow us to attempt the preparation of trichoviridin from such an intermediate and we are currently investigating this approach..

VINYL FORMAMIDE	EPOXY ISONITRILE	% Yield Epoxy Isonitrile	% Yield Vinyl Isonitrile
 <p>NHCHO</p>	 <p>NC</p>	36	22
 <p>NHCHO</p> <p>Cl</p>	 <p>NC</p> <p>Cl</p>	43	17
 <p>NHCHO</p> <p>Br</p>	 <p>NC</p> <p>Br</p>	41	8
 <p>NHCHO</p> <p>NC</p>	 <p>NC</p> <p>NC</p>	68	-
 <p>NHCHO</p>	 <p>NC</p>	30	16
 <p>NHCHO</p> <p>Ph</p>	 <p>NC</p> <p>Ph</p>	33	8

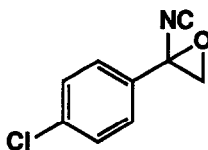


(8)

Acknowledgement: We thank the SERC for the financial support of this work.

#### References

1. Present address, Robert Robinson Laboratories, Dept. of Chemistry, Univ. of Liverpool, P.O. Box 147, Liverpool L69 3BX.
2. J.E.Baldwin, D.J.Aldous, C.Chan, L.M.Harwood, I.A.O'Neil and J.M.Peach, *Synlett*, 1989, **1**, 9. and references therein.
3. Schollkopf has reported the preparation of a functionalized epoxy isonitrile by the conjugate addition of hydroperoxide to an isonitrile substituted acrylate. See I.Hoppe and U.Schollkopf, *Liebigs Ann. Chem.*, 1984, 608.
4. W.L.Parker, M.L.Rathnum, J.H.Johnson, J.Scott Wells, P.A.Principe and R.B.Sykes *J.Antibiotics*, 1988, **41**, 454.
5. A.E.Derome, D.Phil Thesis, University of Oxford, 1982.
6. I.Ugi, "Isonitrile Chemistry," Academic Press, New York, 1971.
7. D.H.R.Barton, W.B.Motherwell and S.Zard, *J.C.S.Chem. Commun.*, 1981, 774.  
H.Ruschig, W.Haede, J.Schmidt - Thome and W.Haede, *Chem.Ber.*, 1955, **88**, 883.
8. For a recent review see, W.Adam, R.Curci and J.O.Edwards, *Acc.Chem.Res.*, 1989, **22**, 205.
9. P.E.Eaton and G.E.Wicks, *J.Org.Chem.*, 1988, **53**, 5353. and P.E.Eaton and G.E.Wicks, *Tetrahedron Lett.*, 1989, **30**, 257.
10. H.K.Chenault and S.J. Danishefsky, *J.Org.Chem.*, 1989, **54**, 4249.
11. J.E.Baldwin and I.A.O'Neil, manuscript in preparation.
12. Y.Ito, A.Ohnishi and M.Murakami, *Synthesis*, 1988, 714.  
R.Appel, R.Kleinstuck and K.D.Ziehn, *Angew.Chem.Int.Ed.Eng.*, 1971, **10**, 132.  
G.Giesmann, E.Von Hinrichs and I.Ugi, *J.Chemical Res.*, 1982, 79.
13. Data for 1- (4'-chlorophenyl)-1-epoxy-1-isocyanoethane:



$^1\text{H-NMR}$  (200MHz): 3.08 (1H, d,  $J = 5.1\text{Hz}$ ), 3.60 (1H, d,  $J = 5.1\text{Hz}$ ), 7.42 (4H, s).  
 $\nu_{\text{max}}$  ( $\text{CCl}_4$ )  $2130\text{ cm}^{-1}$ .  $m/z$  ( $\text{Cl} / \text{NH}_3$ ) 197 ( $\text{M}^+ + \text{NH}_4$ ), 180 ( $\text{M}^+ + \text{H}$ ), 153 ( $\text{M}^+ - \text{NC}$ ).

(Received in UK 19 February 1990)