Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 9299–9302

TETRAHEDRON LETTERS

Ring opening reactions of quinoline substituted epoxides

Andrew N. Boa,* Stephen Clark, Paul R. Hirst and Robert Westwood†

Department of Chemistry, University of Hull, Cottingham Road, Hull HU6 7RX, UK

Received 4 September 2003; revised 3 October 2003; accepted 10 October 2003

Abstract—6-Oxiranyl- and 3-oxiranyl-2-phenylquinoline-4-carboxylic acid diisopropylamides react with secondary amines and lithium amides to give (aminohydroxyethyl)quinolines but with opposite regioselectivities. Upon epoxidation of 3-formylquinoline **2** a ~5:1 mixture of atropisomers is formed. This ratio is maintained upon epoxide ring-opening with amines in ethanol at reflux, but with lithium amides at room temperature a 1.3:1 ratio of isomers is obtained.

Brequinar sodium is a quinoline-4-carboxylate derivative originally described[1] by researchers at DuPont (Fig. 1). This molecule has been shown to be an inhibitor of human dihydroorotate dehydrogenase (DHOdehase), the fourth enzyme involved in the biosynthetic pathway to pyrimidine nucleotides in prokaryotic and eukaryotic organisms.[2] As such, selective inhibitors of this enzyme have a wide range of potential therapeutic applications[3] although development of brequinar as an anticancer agent was halted due lack of efficacy at doses where toxic effects began to appear. We have however been preparing and screening brequinar-related compounds to probe the active site of DHOdehase from a variety of organisms.[4]

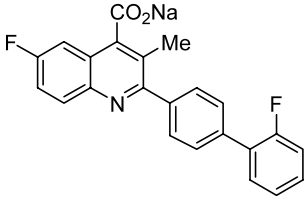
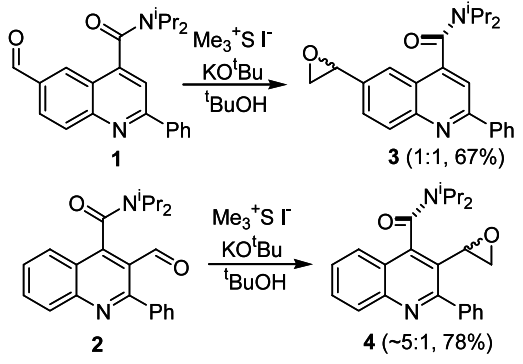


Figure 1. Brequinar sodium.

During the early part of this work we prepared the aldehydes **1** and **2** via free radical bromination followed by oxidation[5] of the corresponding methyl substituted 2-phenylquinoline-4-carboxamide. These aldehydes were chosen to serve as one of several versatile precursors to a wide range of 3- and 6-substituted quinolines.

Conversion of the aldehydes **1** and **2** to their corresponding epoxides **3** and **4** proceeded cleanly using dimethylsulphonium methylide in *tert*-butanol at 30°C (Scheme 1). ^{1}H NMR showed epoxide **3** to be a 1:1 mixture of diastereoisomeric conformers, distinguishable on the NMR timescale due to the restricted rotation about the C_{Ar}–C=O bond. The ^{1}H NMR of epoxide **4** however showed a mixture of isomers ranging from about 5 to 6:1. In 2-substituted 1-naphthoic acid diisopropylamides the rotation about the C_{Ar}–C=O bond is heavily restricted,[6] so the related diisopropylamide **4** can be considered to be a mixture of atropisomers[7] (diastereoisomeric conformers with a half-life of 1000 s or more).



Scheme 1.

Clayden[6] has invoked a non-chelation controlled pathway to explain the reactivity of 2-formylnaphthalene-1-

Keywords: regioselective; epoxide; amino alcohol; atropisomers.
* Corresponding author. Tel.: +44-1482 465022; fax: +44-1482-466410; e-mail: a.n.boa@hull.ac.uk

† Current address: Cyclacel Limited, James Lindsay Place, Dundee Technopole, Dundee DD1 5JJ, UK; bwestwood@cyclacel.com

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.10.062

carboxamides with organometallic reagents under non-chelation control, with attack of the nucleophile on the aldehyde in either the *s-cis* or *s-trans* conformation but always *anti* to the isopropyl groups. The absence of chelating metals in our epoxidation reaction would suggest that ours is a comparable reaction. Molecular modelling[8] indicated that the two conformations of the aldehyde, *s-trans*-**2** and *s-cis*-**2**, were of very similar energy (Fig. 2). Assuming the sulphur ylid attacks either conformation of the aldehyde equally well (on the face opposite to the diisopropyl group), it is not immediately clear therefore why a ~5:1 ratio of products is obtained. In order for a >1:1 isomer ratio to be obtained we presume the initial addition of the sulphur ylid must be reversible allowing the betaines to revert to the aldehyde and ylid. The steric hindrance from the diisopropyl and phenyl substituents would suggest that one of the betaine intermediates requires less energy to adopt the *anti*-conformation needed for epoxide formation and so eliminates dimethyl sulphide more quickly than the other resulting in the ~5:1 epoxide ratio observed.

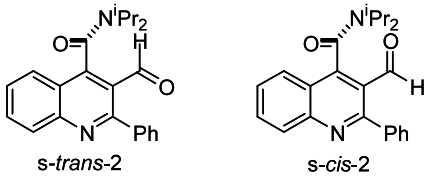
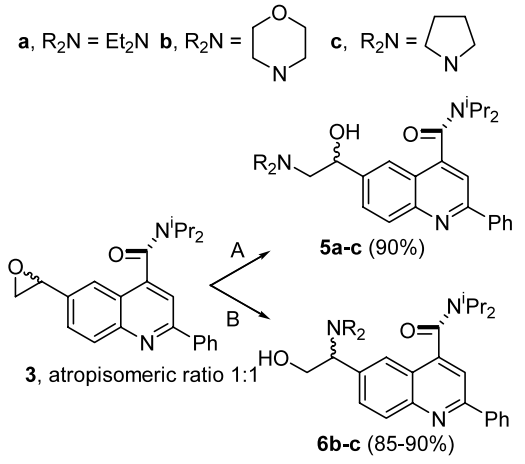


Figure 2. Conformations of aryl aldehyde **2**.

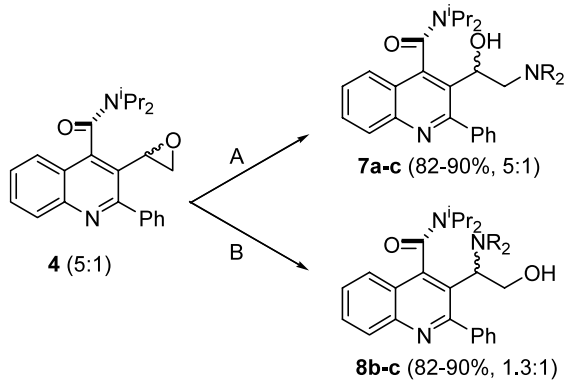
Our reason for preparing the epoxides **3** and **4** was for them to serve as precursors to hydroxyethylquinolines through nucleophilic ring opening of the epoxides. In the case of epoxide **3**, reaction with secondary amines in ethanol gave the expected 6-(2′-amino-1′-hydroxyethyl)quinolines **5** along with the opposite regioisomer **6** as a minor product (~10:1) (Scheme 2). The regioisomers **5** and **6** were separated easily by column chromatography, and in each case ^{1}H NMR showed a 1:1 ratio of diastereoisomeric conformers. Reaction of **3** with lithium amides at room temperature however gave exclusively the regioisomer **6**. Unusually the reaction of **3** with lithium diethylamide was unsuccessful, and starting material was recovered in good yields, even after 24 h. Structural assignments of **5** and **6** were confirmed by correlating literature ^{1}H NMR data of aryl β-amino alcohols.[9] Additionally **6b** was oxidised slowly (PCC, DCM, rt) to give an unstable aldehyde (*H*C=O, δ 10.15 in $CDCl_3$) as opposed to the ketone that would be expected from **5b**.

A report from Singaram and co-workers described reactions of styrene oxide with lithium amides which gave only the 2-dialkylamino-1-phenylethanols,[10] rather than the opposite regiosiomer that we observed. A mechanism involving attack of the nucleophile via initial addition to the carbonyl group then transfer to the epoxide might explain this difference, though we saw no evidence of products in which the diisopropyl amide had been replaced, for example, by a morpholinyl amide. Variable trace lithium halides present in the butyl lithium used to generate the lithium amide could be the source of this dramatic reversal, though Harris and co-workers made and used lithium amides in situ from butyl lithium as well. Chini and co-workers[11] described that heating styrene oxide with diethylamine in ethanol gave a similar regiochemical result to our reactions under the same conditions, and that addition of various soluble lithium salts to the reaction can begin to reverse the regiochemical trend, though not as dramatically as in our case. The participation of the lithium ion coordinating the epoxide oxygen and an incipient benzylic carbocation was used to explain this trend. This same reason can be invoked to explain our result, though the degree of regioselectivity (regiospecificity) is still rather surprising and remains, as yet, unexplained. The presence of the carboxamide function is clearly a main difference in the substrates and so further investigations will be necessary to make firmer conclusions on the generality of these results.

In transferring the reactions from **3** to **4** further observations concerning the reactivity of these epoxides towards amines and lithium amides were made (Scheme 3). Taking a 5:1 mixture of isomeric epoxides **4**, the



Scheme 2. *Reagents and conditions*: Pathway A: R_2NH, EtOH, heat, 2 h: **5a**:**6a** = 12:1; **5b**:**6b** 10:1; **5c**:**6c** 8:1. Pathway B: R_2NLi, THF, rt, 0.5 h: **5**:**6** = 0:1 in all cases.



Scheme 3. *Reagents and conditions*: Pathway A: R_2NH, EtOH, heat, 4–16 h: **7**:**8** = 1:0 in all cases. Pathway B: R_2NLi, THF, rt, 1 h: **7**:**8** = 0:1 in all cases.

reaction with all three secondary amines in ethanol gave the amino alcohols **7a–c**, this time exclusively as might be expected due to the increased steric hindrance at the reaction centre. The 5:1 diastereoisomeric ratio appeared to be retained in the product amino alcohols as shown by ^{1}H NMR of the crude mixtures. The major isomer of amino alcohol **7b** was purified from its atropisomer by fractional crystallisation and single crystal X-ray diffraction[12] proved the regiochemical path of ring opening. However, in one sample of epoxide **4** where the product was initially isolated as a 5.9:1 mixture of atropisomers, heating in toluene at reflux in the absence of a secondary amine for 30 min reduced this ratio to 2:1. Taking this 2:1 isomeric mixture through to the amino alcohol **7b** by treatment with morpholine under the conditions described above, ^{1}H NMR now indicated that the 2:1 diastereoisomeric ratio of the starting material was converted back to a $\sim$5:1 ratio in the product. When the purified major atropisomer of **7b** from the crystallisation study was heated at reflux in ethanol for 6 h, subsequent evaporation of the solvent and analysis of the resulting material indicated that no isomerism had taken place. This indicates that the 5:1 ratio observed in the product amino alcohol must represent the kinetic atropisomeric product ratio of the amino alcohols **7**.

From the X-ray crystal structure of **7b** the relative stereochemistry of the stereogenic axis and centre (Fig. 3) of the major atropisomer was also identified. However, due to the fact that isomerisation of the epoxide takes place so readily in toluene at reflux, this crystal structure sheds no further light on the stereoselectivity of the epoxidation reaction.

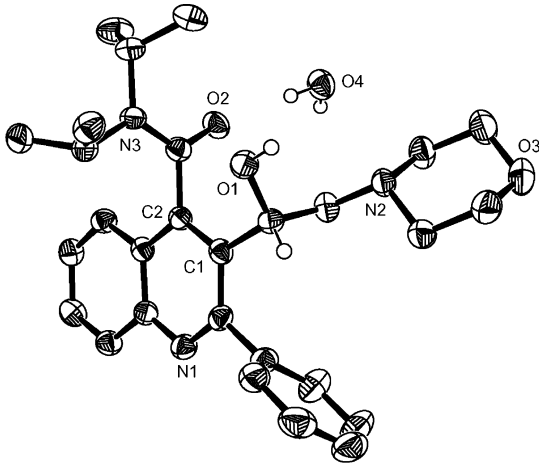


Figure 3. ORTEP view[13] of the amino alcohol **7b** with a water of crystallisation (50% probability ellipsoids and selected hydrogen atoms omitted for clarity).

Reaction of **4** (5:1 atropisomer ratio) with the lithium amides again gave the regioisomer **8** exclusively, as might have been expected based on the precedence of epoxide **3**. However, the atropisomeric mixture in this case was only 1.3:1. Given that these reactions were conducted at room temperature over a short period, it is highly unlikely that the atropisomers of amino alcohol **8** interconvert under these conditions. This result therefore lends credence to the idea that a benzylic carbocation is involved in the reaction under these conditions. In this scenario the lithium ion can coordinate both epoxide and carbonyl oxygen and this would explain both the regiospecificity of the transformation and the reduction in atropisomeric ratio of the product.

Conclusion

In conclusion, we report some interesting stereoselective reactions of atropisomeric epoxides in which the regiochemistry of ring-opening is determined by selection of either an amine or lithium amide. These reactions should be readily extended to aldehydes and ketones in both benzamide and naphthamide series, where the conformational preferences may be much more distinct.[14] Given that aryl amino alcohols and related systems are found often as ligands in metal catalyst systems and in biologically active molecules, the chemistry reported herein could ultimately provide useful methodology for the stereoselective preparation of such molecules.

Acknowledgements

We thank the Engineering and Physical Sciences Research Council (UK) for financial support of this work by providing funds for the purchase of a new X-ray diffractometer and a studentship (P.R.H.).

References

1. Dexter, D. L.; Hesson, D. P.; Ardecky, R. J.; Rao, G. V.; Tippett, D. L.; Dusak, B. A.; Paull, K. D.; Plowman, J.; DeLarco, B. M.; Narayanan, V. L.; Forbes, M. *Cancer Res.* **1985**, *45*, 5563.
2. Jones, M. E. *Annu. Rev. Biochem.* **1980**, *49*, 253.
3. Batt, D. G. *Exp. Opin. Ther. Patents* **1999**, *9*, 41.
4. Boa, A. N.; Hirst, P. R.; Fishwick, C. W. G.; McConkey, G. A.; Ramsey, C. G. C.; Stead, A. M. W., manuscript in preparation.
5. Hass, H. B.; Bender, M. L. *J. Am. Chem. Soc.* **1949**, *71*, 1767.
6. Clayden, J.; McCarthy, C.; Westlund, N.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1363 and references cited therein.
7. Oki, M. *Topics Stereochem.* **1983**, *14*, 1.
8. Molecular mechanics (MM2) modelling studies were performed with CS Chem3D Pro v 5.0 CambridgeSoft Corporation).
9. The chemical shift of the benzylic proton in **5** and **7** occur in the range δ 4.81–5.00, whereas in **6** and **8** it was δ 3.91–4.16 (in $CDCl_3$). These values are consistent with data from numerous examples of phenylethyl amino alcohols in the literature, for example those that can be found in Refs. 10 and 11.

10. Harris, C.; Fisher, G. B.; Beardsley, D.; Lee, L.; Goralski, C. T.; Nicholson, L. W.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 7746.
11. Chini, M.; Crotti, P.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 5939.
12. Crystal data for **7b**: Colourless crystal (0.26×0.25×0.12 mm) from methanol–water, coated with perfluoropolyether oil mounted on a glass fibre, $C_{28}H_{37}N_3O_4$, $M=479.61$, monoclinic, space group $P21/c$, $a=9.6304(14)$, $b=25.463(4)$, $c=11.1929(17)$ Å, $\beta=107.481(11)°$, $V=2618.0(7)$ Å^3, $T=150(2)$ K, $Z=4$, $D_c=1.217$ g cm^{-3}, μ(Mo-Kα)$=0.082$ mm^{-1}, 24450 reflections measured, 7383 unique ($R_{int}=0.0912$) which were used in all calculations. $R_1=0.0383$ on $F>4\sigma(F)$, $wR_2=0.0837$ on all data. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre, reference CCDC 220980.
13. ORTEP3 for Windows: Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.
14. Clayden, J.; Westlund, N.; Beddoes, R. L.; Helliwell, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1351.