A Synthetic Route to *anti* Aminoalkyl Epoxides by Stereocontrolled Reductive Amination of Ketoepoxides

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anti-Aminoalkyl epoxides are synthesized in an enantiomerically pure form by stereoselective reductive amination of ketoepoxides derived from methyl glycidate with tetramethylammonium triacetoxyborohydride.

Protected aminoalkyl epoxides[1] or azidoalkyl epoxides[2] have attracted considerable attention owing to their role in the synthesis of pharmacologically important compounds such as amino sugars, oxygenated amino acids or dipeptides isosteres.[3]

In relation to our studies on the stereoselective opening of epoxides by enolates and application to the synthesis of hydroxymethylene isosteres which play a prominent role as transition-state mimics in inhibitors of aspartic preoteases such as renin[4] or HIV-1,[5] we were interested in finding a versatile method for the synthesis of aminoalkyl epoxides which avoids the use of rather sensitive α-amino aldehydes as the intermediates.

An alternative approach should be offered by the reduction of epoxyimines; however, little is known about the preparation of such compounds, and, due to the great reactivity of monosubstituted epoxides with nucleophiles, epoxyimines derived from epoxy ketones **1** are not available by direct reaction with amines. To circumvent this problem we thought that it might be possible to use a reductive amination which allows a direct path from ketones to amines.

We report here an efficient and stereospecific route to aminoalkyl epoxides by reductive amination of enantiomerically pure ketoepoxides.

Reductive amination of aldehydes or ketones is generally achieved by using sodium cyanoborohydride with an ammonium salt.[6] However, in our work, we desired a hydride alternative which would allow the direct formation of a *N*-protected amino epoxide. More recently, it was shown that the use of sodium triacetoxyborohydride allowed such a reduction with primary amines.[7]

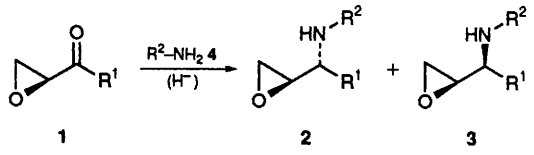
Accordingly, a mixture of epoxy ketone **1** (R^1 = Bu^i) and benzylamine was reacted with sodium triacetoxyborohydride in the presence of acetic acid. The result, however, was not promising. After aqueous work-up, a 9:1 mixture of diastereoisomers **2** and **3** was isolated in a rather poor yield (29%) in addition to the *N*-benzyl aziridine **5** (32% yield) resulting from an intramolecular attack of the epoxide moiety. Surprisingly, the amino alcohol resulting from the opening of the epoxide by benzylamine was not observed. In light of this result, we decided to use a very mild and more selective reagent: tetramethylammonium triacetoxyborohydride.[8] Indeed, with this reagent, we succeeded in avoiding almost completely the formation of the aziridine, and the epoxy amines **2** and **3** were isolated in 68% yield.

This reaction was then applied to various optically active keto epoxides. Such compounds may be synthesized by oxidation of epoxy alcohols obtained by kinetic resolution of secondary allylic alcohols[9] or rearrangement of primary epoxy alcohols.[10] More easily, we prepared them by reaction of optically pure methyl glycidate derived from L- or D-serine[11] with organolithium compounds at low temperature.[12]

Except for the methyl substituted ketone (entry 1), we observed in all cases a high stereoselectivity in favour of the *anti* isomer (Table 1). Satisfactory results were also obtained with allylmine the use of which may provide an alternative method for obtaining protected amines.

To determine the stereochemistry of the reduction, the epoxy amine **2a** was open by catalytic hydrogenation and the resulting amino alcohol reacted with phosgene to give the oxazolidinone **6**. Analysis of the ^{1}H NMR spectrum showed the coupling constant $J_{4,5}$ to be 7.5 Hz suggesting it to be a *cis* isomer, the coupling constants being slightly smaller for *trans* oxazolidinones than those observed for *cis* isomers.[13] An unambiguous stereoassignment was obtained from comparison of proton NMR data of amino epoxides **2** and **3** and the *syn* compounds synthesized by reaction of benzylamine with the *anti* trifluoromethanesulfonates (Tf) **7** derived from the corresponding *anti* epoxy alcohols.[14]

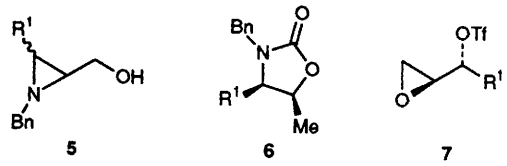
The enantiomeric purity of **3a** has been verified to be >98% by chiral chromatography of the oxazolidinone **6** (XE-60 *S*-valine-*S*-α-pea Chrompack column) indicating that the optical



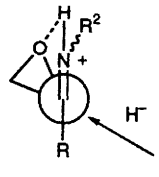
1 **2** **3**

a; R^2 = Bn
b; R^2 = allyl

Scheme 1



5 **6** **7**



Scheme 2

Table 1 Diastereoselective aminating reduction of keto epoxides

Entry	Keto epoxide **1**(R^1)	Amine **4**	2 *anti*:3 *syn* Ratio[b] (% yield)[c]	$2[\alpha]_D^{20}$ (*c*, CH_2Cl_2)
1	Me	**a**	72:28 (69)	
2	Pr^i	**a**	93:7 (33)	−2.9 (2.26)
3	Pr^i[a]	**b**	91:9 (30)	
4	Bu^i	**a**	92:8 (68)	+17.6 (2.25)
5	Bu^i[a]	**b**	93:7 (55)	
6	Ph–CH_2	**a**	94:6 (57)	+12.3 (2.24)
7	C_6H_{11}–CH_2	**a**	95:5 (56)	+14.3 (2.27)

[a] Racemic substrate. [b] Determined by HPLC and 250 MHz ^{1}H NMR spectroscopy. [c] Combined, isolated yields of **2** and **3**. Typical procedure: To a mixture of keto epoxide **1** (1 mmol), amine **4** (1.3 mmol) and acetic acid (1.3 mmol) in 1,2-dichloroethane was added tetramethylammonium triacetoxyborohydride and 4 Å molecular sieves (0.5 g). After stirring for 8 h at room temp., the mixture was hydrolysed (K_2CO_3 1 mol dm^{-3}) and purified.

purity of the starting glycidic epoxide was completely retained during the reactions.

The stereochemistry of this reduction may be interpreted by the formation during the transition state of an internal hydrogen bond between the hydrogen of the iminium salt and the oxygen of the epoxide ring which blocks the conformation (Scheme 2). Hydride attack from the less hindered face then gives rise to the observed products.

This model is in accordance with the recent results reported for the addition of nucleophiles to α,β-epoxycarbonyl compounds,[15] *anti* diastereoselection being generally observed during the reaction of epoxy-ketones with reagents susceptible of favouring chelation between the epoxide oxygen and the carbonyl function.[14,16]

Received, 21st September 1993; Com. 3/05710K

References

1 Y. Ohfune and N. Korokawa, *Tetrahedron Lett.*, 1984, **25**, 1587; B. E. Evans, K. E. Rittle, C. F. Homwick, J. P. Springer, J. Hirshfield and D. F. Veber, *J. Org. Chem.*, 1985, **50**, 4615; J. R. Lully, J. F. Dellaria, J. J. Plattner, J. L. Soderquist and N. Yi, *J. Org. Chem.*, 1987, **52**, 1487; M. T. Reetz and J. Binder, *Tetrahedron Lett.*, 1989, **30**, 5425.

2 M. Bessodes, E. Abushanab and K. Antonakis, *Tetrahedron Lett.*, 1984, **25**, 5899; A. K. Ghosh, S. P. McKee, H. E. Lee and W. J. Thompson, *J. Chem. Soc., Chem. Commun.*, 1992, 273; F. Bennett, V. M. Girijavallabhan and N. Patel, *J. Chem. Soc., Chem. Commun.*, 1993, 737.

3 K. T. Shaw, J. R. Luly and H. Rapoport, *J. Org. Chem.*, 1985, **50**, 4515; W. R. Roush, J. A. Staub and R. J. Brown, *J. Org. Chem.*, 1987, **52**, 5127; D. Askin, M. A. Wallace, J. P. Vacca, R. A. Reamer, R. P. Volante and I. Shinkai, *J. Org. Chem.*, 1992, **57**, 2771.

4 W. J. Greenlee, *Pharmaceutical Res.*, 1987, **28**, 263; D. H. Rich, in *Comprehensive Medicinal Chemistry*, ed. P. G. Sammes, Pergamon Press, Oxford, 1992, vol. 2, pp. 391–441; W. J. Greenlee, *J. Med. Res. Rev.*, 1990, **10** 173 and references cited therein.

5 J. R. Huff, *J. Med. Chem.*, 1991, **34**, 2305.

6 C. F. Lane, *Synthesis*, 1975, 135; R. O. Hutchins and N. Natale, *Org. Prep. Proced. Int.*, 1979, **11**, 20.

7 A. F. Abdel-Magid, C. A. Maryanoff and K. G. Carson, *Tetrahedron Lett.*, 1990, **31**, 5595.

8 D. A. Evans, K. T. Chapman and E. M. Carreira, *J. Am. Chem. Soc.*, 1988, **110**, 3560.

9 Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765.

10 J. M. Palazon, B. Anorbe and V. S. Martin, *Tetrahedron Lett.*, 1986, **27**, 4987.

11 M. Larchevêque and Y. Petit, *Bull. Soc. Chim. Fr.*, 1989, 130.

12 To be published; an analogous reaction was previously used for the synthesis of *O*-protected α-hydroxyketones: M. Larchevêque and Y. Petit, *Synthesis*, 1986, 60.

13 T. A. Foglia and D. Swern, *J. Org. Chem.*, 1969, **34**, 1680; D. R. Williams, M. H. Osterhout and J. P. Reddy, *Tetrahedron Lett.*, 1993, **34**, 3271.

14 T. Nakata, T. Tanaka and T. Oishi, *Tetrahedron Lett.*, 1981, **22**, 4723.

15 G. P. Howe, S. Wang and G. Procter, *Tetrahedron Lett.*, 1987, **28**, 2629; H. Iio, T. Misobuchi and T. Tokoroyama, *Tetrahedron Lett.*, 1987, **28**, 2379; W. R. Roush, J. A. Straub and M. S. Van Nieuwenhze, *J. Org. Chem.*, 1991, **56**, 1636; J. M. Escudier, M. Baltas and L. Gorrichon, *Tetrahedron Lett.*, 1992, **33**, 1439; H. Urabe, T. Matsuka and F. Sato, *Tetrahedron Lett.*, 1992, **33**, 4179; K. J. M. Beresford, G. P. Howe and G. Procter, *Tetrahedron Lett.*, 1992, **33**, 3355.

16 S. Okamato, H. Tsujiyama, T. Yoshino and F. Sato, *Tetrahedron Lett.*, 1991, **32**, 5789; H. Urabe, Y. Aoyama and F. Sato, *J. Org. Chem.*, 1992, **57**, 5056.