Tetrahedron Letters, Vol. 33, No. 23, pp. 3281-3284, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

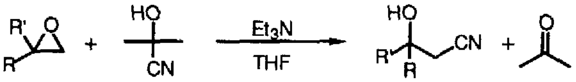
Regiospecific Opening of 1,2-Epoxides with Acetone Cyanohydrin under Mildly Basic Conditions

David Mitchell* and Thomas M. Koenig

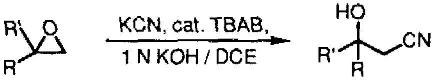
Lilly Research Laboratories, Eli Lilly and Company
Lilly Corporate Center, Indianapolis, Indiana 46285

Abstract: Acetone cyanohydrin with stoichiometric triethylamine opens epoxides regiospecifically to give β-hydroxy nitriles. As expected, addition of cyanide occurs at the least substituted carbon.

The possibility of utilizing a nucleophilic cyanide addition to an epoxide to provide a β-hydroxy nitrile has been recognized[1]. During studies directed towards this goal, we encountered difficulties in using literature methods[2] for direct nucleophilic cyanide addition. The two major disadvantages were regioselectivity[2c] and isolation of water soluble products. It should be noted that trimethylsilyl cyanide has been used to open epoxides to provide β-siloxy nitriles[3]. We report herein the regiospecific synthesis of some β-hydroxy nitriles from 1,2 epoxides and acetone cyanohydrin.

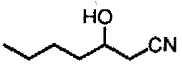
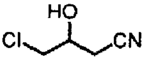
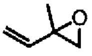
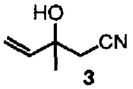
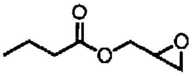
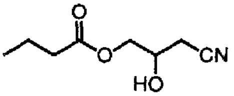
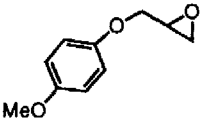
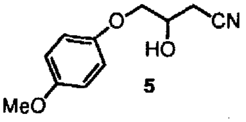
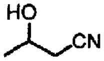
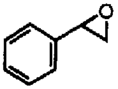
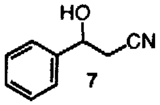
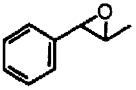


Initial attempts to open epoxides under phase transfer conditions[4] using catalytic tetrabutylammonium bromide and potassium cyanide gave good results. For example, when epoxyhexane and potassium cyanide were reacted with 1.0 % molar tetrabutylammonium bromide, an 84 % of 3-hydroxy heptanenitrile was obtained. Unreacted epoxide was always recovered in some cases even after long reaction periods. It has been reported that cyanide ion in conjuction with acetone cyanohydrin is a hydrocyanating reagent for α,β-unsaturated carbonyl systems[5]. We anticipated that reaction would proceed to completion by some modification of the cyanide / acetone cyanohydrin reagent. Although there were some improvements in the biphasic system with the



TBAB = tetrabutylammonium bromide; DCE = 1,2-dichloroethane

Table I. Summary of regiospecific opening of epoxides with acetone cyanohydrin

Entry	Epoxide	Reaction Time	Product	Yield[a]
1)		3.0 h	 **1**	74 %
2)		3.5 h	 **2**	67 %
3)		4.0 h	 **3**	63 %
4)		3.5 h	 **4**	91 %
5)		13.0 h	 **5**	87 %
6)		3.0 h	 **6**	76 %
7)		18.0 h	 **7**	88 %
8[b])		18.0 h	NR	–
9[b])		18.0 h	NR	–

a = The yields which are reported correspond to isolated products, which have been purified using silica gel chromatography, distillation or recrystallization. b) NR = no reaction; 83 % of phenylpropylene oxide was recovered ; 74 % of cyclohexene oxide was recovered.

aid of acetone cyanohydrin, the difficult task of isolating water soluble products remained a problem.

Since acetone cyanohydrin was a good source of cyanide ion[5a], we proposed a homogeneous reaction involving stoichiometric acetone cyanohydrin under mildly basic conditions for epoxide ring opening. This reaction proceeded as anticipated: when epoxyhexane was refluxed with stoichiometric triethylamine and acetone cyanohydrin in THF for 4 h, 3-hydroxyheptanenitrile was isolated as the only product. Systemic investigation of this procedure using various epoxides (Table I entries 1-9)[6] reveal the method to be general for acyclic 1,2-epoxides.

As can be observed, nucleophilic addition occurred only at the least substituted carbon of the epoxide. Only one regioisomer was observed in every reaction[7] (entries 1-7). Functional groups such as simple esters and chlorine are stable under the reaction conditions. Geminally disubstituted epoxides undergo regiospecific ring opening as well to provide β-hydroxy nitriles in high yield (entry 3). In addition, the reaction is chemoselective in that no β-hydroxy nitriles were observed for vicinally substituted epoxides (entries 8 and 9). Only unreacted epoxide was isolated when cyclohexane oxide or phenyl propylene oxide was used.

A full equivalent of base is not required for complete reaction, rendering the process catalytic in base. Detail mechanistic aspects will be discussed in a later publication. This new method for preparation of β-hydroxy nitriles from 1,2-epoxides has advantages in that acetone cyanohydrin is readily available[8], does not require metallic salts, does not require high boiling polar aprotic solvents and good to excellent yields of products are obtained.

A typical experimental procedure for the preparation of **1** (Table I) is as follows: acetone cyanohydrin (10.1 g, 119 mmol), 1,2-epoxyhexane (10.0 g, 100 mmol) and triethylamine (12.0 g, 119 mmol) were refluxed with stirring for 4 hr in 40 mL of THF under a nitrogen atmosphere. The mixture was cooled, diluted with water (40 mL) and extracted twice with ethyl ether. After drying over magnesium sulfate, the combined organic layers were concentrated under vacuum, and the residue distilled (120 °C /13 mm) to provide 9.5 g (74 %) of a clear, colorless oil; TLC R_f 0.67 (Et_2O); IR (neat) cm^{-1} 3610, 3462, 3019, 2260, 1243; ^{1}H NMR ($CDCl_3$) δ 3.87 (qn, J = 5.71 Hz, 1H), 3.12 (bs, 1H), 2.51(m, 2H), 1.59 (m, 2H), 1.28 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}H NMR ($CDCl_3$) δ 118.1, 67.7, 36.2, 27.3, 26.1, 22.4, 13.9; Anal Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.72; H, 10.43; N, 11.07. When the product is water soluble such as **2** and **3**, the reaction mixture is simply concentrated and the residue distilled to obtain the product.

Acknowledgements: We are grateful to Dr. B. G. Jackson for helpful discussions and the Lilly Physical Chemistry group for providing analytical and spectral data.

References and Notes

1. a) Ko, S. Y., Masamune, H., Sharpless, K. B., *J. Org. Chem.* **1987**, 52, 667. b) Klunder, J. M., Onami, T., Sharpless, K. B. *J. Org. Chem.* **1989**, 54, 1295.

2. a) Smiley, R. A., Arnold, C. *J. Org. Chem.* **1960**, 25, 257. b) Zubrick, J. W., Dunbar, B. I., Durst, H. D. *Tetrahedron Lett.* **1975**, 71. c) Nagata, W., Yoshioka, M., Okamura, T. *J. Chem. Soc. C.* **1970**, 2365.

3. a) Sugita, K., Akihisa, O., Makoto, O., Yusuke, I. *Chemistry Lett.* **1990**, 3, 481. b) Sassaman, M. B., Prakash, G. K. S., Olah, G. A. *J. Org. Chem.* **1990**, 55, 2016.

4. Similar phase transfer cyanide addition in the preparation of benzoyl cyanides have been reported: Koenig, K. F., Weber, W. P. *Tetrahedron Lett.* **1974**, 26, 2275.

5. a) Liotta, C. L., Dabdoub, A. M., Zalkow, L. H. *Tetrahedron Lett.* **1977**, 13, 1117. b) Rahm, A., Guilhemat, R., Pereyre, M. *Syn. Comm.* **1982**, 12, 485.

6. All new compounds presented correct composition by elemental analysis and spectral data in accordance with the proposed structure.

7. The regioisomeric assignment of the products was determined by ^{1}H and ^{13}C NMR (300 MHz). For example, in the case of **1**, the characteristic signal for the a methylene group (C-2) was observed at 2.51 ppm in the ^{1}H NMR spectrum.

8. Acetone cyanohydrin is readily available from Aldrich Chemical Company or Fluka Chemical Corp.

(Received in USA 11 March 1992)