Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 7355–7358
Tetrahedron Letters

Highly regioselective ring opening of epoxides using NaN_3: a short and efficient synthesis of (−)-cytoxazone

Joshodeep Boruwa, Jagat C. Borah, Biswajit Kalita and Nabin C. Barua*

Natural Products Chemistry Division, Regional Research Laboratory (CSIR), Jorhat 785006, Assam, India

Received 14 June 2004; revised 20 July 2004; accepted 30 July 2004
Available online 20 August 2004

Abstract—A convenient and efficient synthesis of 1,2-azido alcohols has been achieved by regioselective ring opening of epoxides using NaN_3 and 4 Å molecular sieves in acetonitrile. The utility of this method has been demonstrated by achieving a short synthesis of (−)-cytoxazone in 48% overall yield.

1,2-Azidoalcohols are versatile intermediates in organic synthesis, since they are important precursors of β-aminoalcohols and vicinal diamines, which are present in numerous natural products.[1] Furthermore, their importance is significant in the chemistry of carbohydrates and nucleosides.[2] Since the discovery of Sharpless asymmetric epoxidation[3] and asymmetric dihydroxylation[4] the ring opening reactions of epoxides have been extensively studied in the context of the chiral synthesis of biologically active natural products.

Generally, azidohydrins are prepared through ring opening of epoxides using different azides in suitable solvents. The classical method uses[5] sodium azide and ammonium chloride but it requires a long reaction time (12–48 h) and is often accompanied by isomerization, epimerization and rearrangement of the products.[6a] Hence, several modifications have been made, which include the combined use of NaN_3 or $TMSN_3$ and a Lewis acid or transition metal complex[7] or reaction in the presence of tetrabutylammonium salts.[8] Recently, pH-controlled azidolysis of epoxides was also studied in water using various Lewis acids and NaN_3.[6]

Although these methods have their own advantages, many of them suffer from one or more drawbacks such as long reaction times, strongly acidic conditions, lack of regioselectivity, high cost of reagent, difficulty in work-up and lack of reusability of a catalyst. Therefore a better catalyst that would be superior to the existing ones, especially with regard to recyclability and selectivity, is still required.

In recent years, organic reactions on solid supports such as zeolites or mesoporous molecular sieves[9] have attracted attention because of the advantages these catalysts have, such as high purity of the product, easy work-up procedure, reusability and the environment-friendly nature of the catalyst. In continuation of our interest in the chemistry of epoxides and their application in the synthesis of bioactive natural products,[10] we found that a variety of epoxides can be opened in a regioselective manner with NaN_3 using 4 Å molecular sieves as the catalyst (Table 1).

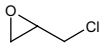
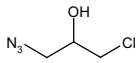
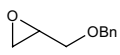
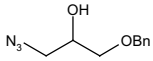
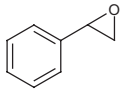
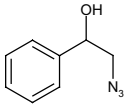
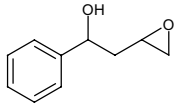
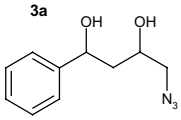
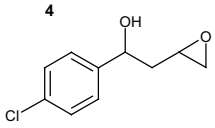
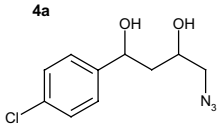
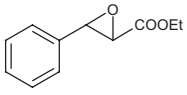
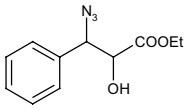
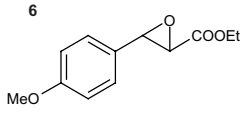
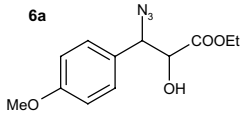
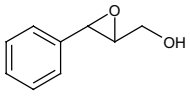
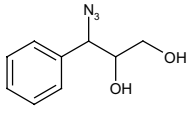
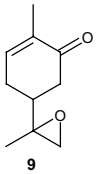
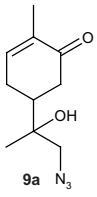
It is evident from Table 1 that in the case of terminal epoxides such as **1**, **2**, **4**, **5** and **9**, the attack by azide nucleophile takes place exclusively at the less hindered position, whereas in the case of α-phenyl epoxides such as **3**, **6**, **7** and **8**, the attack takes place predominantly at the benzylic position, although trace amounts of the other regioisomer were detected in the case of epoxides **6**, **7** and **8**.

In order to compare the regioselectivity of this ring opening reaction, a comparative study was carried out with the classical method. Our findings are shown in Table 2. The high regioselectivity of our catalyst is evident from the yields of the individual regioisomers.

Keywords: Molecular sieves; Azidoalcohol; Regioselectivity; (−)-Cytoxazone.
* Corresponding author. Tel.: +91 376 2370121; fax: +91 376 237 0011; e-mail: ncbarua2000@yahoo.co.in

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.07.157

Table 1. Regioselective ring opening of epoxides using NaN_3/CH_3CN/4 Å MS

Entry	Epoxide	Product	Time (h)	Yield[a] (%)
1	 **1**	 **1a**	1.0	97
2	 **2**	 **2a**	1.2	96
3	 **3**	 **3a**	1.0	96
4	 **4**	 **4a**	1.3	92
5	 **5**	 **5a**	1.5	90
6	 **6**	 **6a**	1.5	94 (3)
7	 **7**	 **7a**	1.6	95 (2)
8	 **8**	 **8a**	1.2	95 (2)
9	 **9**	 **9a**	1.2	92

[a] Yields of pure isolated product. Yields in the parentheses correspond to the yield of the other regioisomer.

The reason for high regioselectivity exhibited by 4 Å molecular sieve in the epoxide opening may be attributed to potassium ion, which is the cation constituent of 4 Å molecular sieves.[11] Finally we turned our attention towards the possible recycling of the catalyst. The catalyst was filtered off, washed with acetone, dried and reused. In these experiments products were obtained in almost the same yields and regioselectivity.

Seeing the near exclusive formation of the regioisomer **7a** (Table 2, entry 4), we decided to employ this method for a synthesis of (−)-cytoxazone **15**, a natural product possessing cytokine modulating activity isolated from *Streptomyces* sp. by Osada and co-workers.[12] It is reported that (−)-cytoxazone exhibits cytokine modulating activity by inhibiting the signalling pathway of Th2 cells[13] and because of interesting biological activity, this molecule has been the target of various recent synthetic efforts.[14] Sunjic and co-workers synthesized this molecule in the optically pure form using a strategy involving epoxide ring opening with NaN_3. However in their synthesis the yield of the desired regioisomer of the azido alcohol was only 56% and to obtain the final product they employed a kinetic resolution step using *Candida antarctica* lipase (CAL).[14b]

We started the synthesis of (4*R*,5*R*)-cytoxazone from ethyl *p*-methoxycinnamate **10**, which was prepared on

Table 2. Comparative results of regioselectivity

Entry	Epoxide	Product	Conditions[a]	Yield[b] (%)
1	**2**	**2a**	A	96
			B	88 (2)
2	**3**	**3a**	A	95 (2)
			B	76 (12)
3	**6**	**6a**	A	94 (3)
			B	78 (13)
4	**7**	**7a**	A	95 (2)
			B	79 (10)
5	**8**	**8a**	A	95 (2)
			B	83 (11)

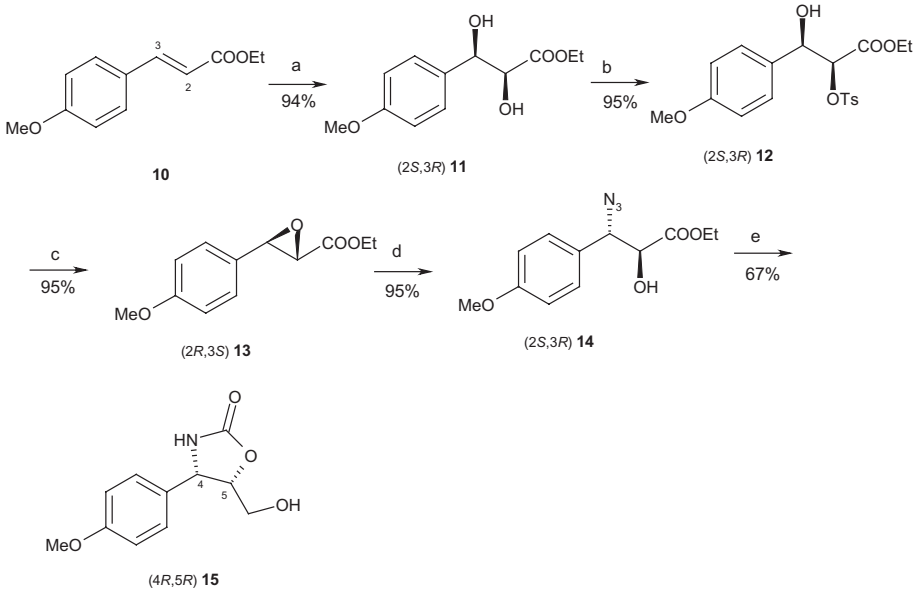
[a] A: 1.5 equiv NaN_3, 4 Å molecular sieves, CH_2Cl_2. B: 2.2 equiv NaN_3, 5 equiv NH_4Cl, $MeOH/H_2O$ (8:1) reflux.
[b] Yields in parentheses are of the other regioisomer.

a large scale in 82% yield by Wittig olefination of *p*-anisaldehyde with triphenyl carbethoxymethyl phosphonium chloride supported on basic alumina under microwave irradiation (Scheme 1).

Instead of resorting to a kinetic resolution step, we decided to construct the epoxide with the desired chirality at this stage. α,β-Unsaturated esters are very good substrates for asymmetric dihydroxylation resulting in excellent enantiomeric excess. Thus when compound **10** when subjected to ADH[4] using $(DHQD)_2PHAL$, diol (2*S*,3*R*)-**11** was isolated in 94% yield and 99% ee[15] as a solid, which was treated with *p*-toluenesulfonyl chloride and triethylamine in dichloromethane[16] to give the monotosylated product (2*S*,3*R*)-**12** as a crystalline solid in 95% yield and 98% ee. The next step in the synthesis was the formation of the epoxide (2*R*,3*S*)-**13**, which was effected by treating (2*S*,3*R*)-**12** with K_2CO_3 in methanol[17] whereupon the epoxide (2*R*,3*S*)-**13** was obtained as a gum in 96% yield and 99% ee without epimerization at the C-2 centre, which is a serious problem with several other base/solvent combinations.[18] Azidolysis of this epoxide was performed with NaN_3 and 4 Å molecular sieves in acetonitrile to obtain the azido alcohol (2*S*,3*R*)-**14** in 95% yield and 98% ee. The carbocationic character in the transition state needed for regioselective attack by the nucleophile, at the benzylic position is encouraged by the electron donating effect of the *p*-methoxy group.[19] Conversion of (2*S*,3*R*)-**14** to (−)-cytoxazone was achieved following the procedure described by Nakata and co-workers[14a] giving (−)-cytoxazone in 48% in overall yield, the spectral data of which were identical to those reported.[12]

In summary we have described a novel procedure for the regioselective ring opening of epoxides, which does not require tedious preparation of the catalyst or harsh conditions like other solid-supported catalysts employed for this purpose. The reusability of this catalyst, high degree of regioselectivity, mild reaction conditions, low cost of the reagent and easy work-up procedure make it an attractive methodology. Further we have described an efficient synthesis of (−)-cytoxazone using this methodology as one of the steps.

Spectral data of some selected compounds: **2a**. IR (chloroform, cm^{-1}): 3420, 2917, 2866, 2101, 1496, 1454, 1279, 1099, 738, 698. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.21$ (5H), 4.43 (s, 2H), 3.81 (m, 1H), 3.45 (d, $J = 4$ Hz, 2H), 2.83 (br s). MS (ESI) $m/z = 230.1$ (M^++Na). Compound **6a**. IR (chloroform, cm^{-1}): 3462, 2983, 2107, 1736, 1736, 1637, 1311, 1256, 1069, 769, 702. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.29$ (5H), 4.85 (d, $J = 2.7$ Hz, 1H), 4.21 (m, 1H), 4.11 (q, $J = 4.4$ Hz, 2H), 1.37 (t, $J = 7.1$ Hz, 3H), 2.11 (br s).



Scheme 1. Reagents and conditions: (a) $(DHQD)_2PHAL$, OsO_4, *t*-BuOH/H_2O (1:1), 0 °C 16 h; (b) TsCl, Et_3N, CH_2Cl_2, 5 °C, 72 h; (c) K_2CO_3, MeOH, rt, 12 h; (d) NaN_3, 4 Å molecular sieves, CH_3CN, rt, 1.6 h; (e) (i) PhCOCl, pyridine, CH_2Cl_2, (ii) PPh_3, THF/H_2O, 50 °C, (iii) $NaBH_4$, MeOH, 0 °C (67% in three steps).

MS (ESI) $m/z = 258.0$ (M^++Na). Compound **8a**. IR (chloroform, cm^{-1}): 3408, 2931, 2103, 1443, 1279, 1104, 944, 873, 771. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.21$ (5H), 4.22 (d, $J = 6$ Hz, 1H), 3.59 (m, 1H), 3.28 (d, $J = 2.6$ Hz, 1H), 2.08 (br s, 1H). MS (ESI) $m/z = 216.0$ (M^++Na).

(2*S*,3*R*)-**11**: Solid; mp: 72–73 °C; $[\alpha]_D^{20}$ −6.1 (*c* 1 methanol); ee: 99%. IR (chloroform, cm^{-1}): 3449, 2982, 2937, 2838, 1735, 1613, 1514, 1465, 1389, 1370, 1302, 1249, 1178, 1031, 834, 771. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.38$ (d, $J = 8.5$ Hz, 2H), 6.84 (d, $J = 8.5$ Hz, 2H), 4.92 (d, $J = 5.5$ Hz, 1H), 4.12 (q, $J = 4.4$ Hz, 2H), 3.85 (s, 3H), 3.25 (d, $J = 5.5$ Hz, 1H), 2.85 (br, 1H), 1.35 (t, $J = 7.17$ Hz, 3H). MS (ESI) $m/z = 263.0$ (M^++Na). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 13.09$, 54.29, 61.11, 73.23, 73.8, 112.8, 124.89, 126.62, 131.07, 158.35, 171.80. Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.80; H, 6.88.

(2*S*,3*R*)-**12**: Solid; mp 97–98 °C; $[\alpha]_D^{20}$ −46 (*c* 1 methanol); ee: 98%. IR (chloroform, cm^{-1}): 3426, 3025, 2930, 1742, 1614,1514, 1370, 1250, 1176, 1030, 882, 767. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.57$ (d, $J = 8.2$ Hz, 2H), 7.19 (d, $J = 8.1$ Hz, 2H), 7.10 (d, $J = 8.6$ Hz, 2H), 6.71 (d, $J = 8.6$ Hz, 2H), 4.98 (d, $J = 4.9$ Hz, 1H), 4.76 (d, $J = 5$ Hz, 1H), 4.03 (q, $J = 7$ Hz, 2H), 3.75 (s, 3H), 2.82 (br, 1H), 2.41 (s, 3H), 0.98 (t, $J = 7$ Hz, 3H). MS (ESI) $m/z = 417.1$ (M^++Na). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 12.81$, 20.63, 54.05, 60.81, 72.26, 75.59, 76.01, 76.44, 80.57, 95.13, 112.64, 126.65, 127.00, 128.48, 128.55, 131.79, 143.67, 158.57, 165.88.

(2*R*,3*S*)-**13**: Gum; $[\alpha]_D^{20}$ +9.1 (*c* 0.8, chloroform); ee: 98%. IR (chloroform, cm^{-1}): 2926, 2936, 2838, 1733, 1612, 1513, 1463, 1301, 1249, 1111, 1030, 833. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.31$ (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 8.5$ Hz, 2H), 4.24 (d, $J = 7$ Hz, 1H), 4.02 (q, $J = 7$ Hz, 1H), 3.82 (d, $J = 4.7$ Hz, 1H), 3.70 (s, 3H), 1.30 (t, $J = 7$ Hz, 3H). MS (ESI) $m/z = 222.0$ (M^+). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.63; H, 6.12.

(2*S*,3*R*)-**14**: Liquid; $[\alpha]_D^{20}$ −23 (*c* 1.0 chloroform); ee: 98%. IR (chloroform, cm^{-1}): 3490, 2965, 2107, 1744, 1612, 1514, 1428, 1252, 1213, 1131, 1028, 827. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.30$ (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 8.5$ Hz, 2H), 4.85 (d, $J = 2.7$ Hz, 1H), 4.23 (q, $J = 7$ Hz, 2H), 3.75 (s, 3H), 3.08 (d, $J = 6.7$ Hz, 1H), 1.30 (t, $J = 7$ Hz, 3H). MS (ESI) $m/z = 265.1$ (M^+). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 12.82$, 54.60, 56.73, 67.45, 77.51, 77.45, 77.85, 112.81, 125.49, 127.13, 156.43, 168.29. Anal. Calcd for $C_{12}H_{15}O_4N_3$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.49; H, 5.83; N, 15.97.

General method for epoxide ring opening: NaN_3 in 2 mL CH_3CN were added to powdered 4 Å molecular sieves (100 mg) and the mixture stirred for specific time. The reaction mixture was then filtered, the filter pad was washed with CH_3CN and the combined filtrates was evaporated. The crude product was then purified by chromatography over silica gel using ethylacetate/petroleum ether as eluent.

Acknowledgements

The authors are thankful to Director R. R. L. Jorhat for providing facilities.

References and notes

1. Schuberet, J.; Schwesinger, R.; Prizbach, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *23*, 167–169.
2. Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368.
3. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5976–5978.
4. Jacobsen, E. N.; Marko, I.; Mungall, S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970.
5. (a) *The Chemistry of Azido Group*; Patal, S., Ed.; Wiley: New York, 1971; (b) Nugent, T. C.; Hudlicky, T. *J. Org. Chem.* **1998**, *63*, 510–520.
6. (a) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *64*, 6094–6096; (b) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 4719–4722.
7. (a) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768–2769; For review: (b) Paterson, L.; Barrisford, D.; Organic, J. In *Synthesis Highlights III*; Mulzer, C., Waldmann, H., Eds.; Wiley: VCH, 1998.
8. Schnieder, C. *Synlett*, **2000**, 1840–1842.
9. Sen, S. E.; Smith, S. M.; Sullivan, K. A. *Tetrahedron* **1999**, *55*, 12657–12698.
10. Kalita, B.; Bezbarua, M. S.; Barua, N. C.; Bez, G. *Synlett*, **2001**, 1411–1414.
11. Paquette, L. A., Ed. Encyclopaedia of Reagents for Organic Synthesis; John Wiley & Sons, 1995; Vol. 5, pp 3646.
12. Kakeya, H.; Morishita, M.; Kobinata, K.; Osono, M.; Ishizuka, M.; Osada, H. *J. Antibiot.* **1998**, *51*, 1126–1128.
13. Kakeya, H.; Morishita, M.; Koshino, H.; Morita, T.; Kobayashi, K.; Osada, H. *J. Org. Chem.* **1999**, *64*, 1052–1053.
14. (a) Sakamoto, Y.; Shiraishi, A.; Soenhee, J.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 4203–4206; (b) Hamersak, Z.; Ljubovic, E.; Mercep, M.; Mesic, M.; Sunjic, V. *Synthesis*, **2001**, 1989–1992; (c) Vanketeswara Rao, B.; Madhan, A.; Kumar, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2009–2011; (d) Miyata, O.; Asai, H.; Naito, T. *Synlett* **1999**, 1915–1916.
15. The enantiomeric excess (ee) was measured by HPLC analysis carried out on a Waters 510 HPLC system. Chiracel OD packed in a SS column of 4.6 mm i.d. × 250 mm dimension was used. Isocratic elution was applied with a mobile phase *n*-hexane 90% and isopropanol 10% at a flow rate 0.8 mL/min, and pressure 125 psi. UV was monitored at 243 nm.
16. Denis, J.-N.; Correa, A.; Green, A. E. *J. Org. Chem.* **1990**, *55*, 1957–1959.
17. Flemming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869–2875.
18. Hoffman, R. V.; Kim, H. *J. Org. Chem.* **1991**, *56*, 6759–6764.
19. (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557–1560; (b) Caron, M.; Carlier, R. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185–5187.