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Ring Opening of Epoxides with Sodium Azide in Water. A Regioselective pH-Controlled Reaction

Francesco Fringuelli,* Oriana Piermatti, Ferdinando Pizzo,* and Luigi Vaccaro

Dipartimento di Chimica, Università degli Studi di Perugia, via Elce di Sotto 8, 06123 Perugia, Italy

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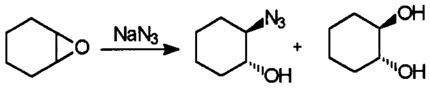
1,2-Azido alcohols are compounds of interest in organic synthesis as either precursors of vicinal amino alcohols or in the chemistry of carbohydrates and nucleosides.[1] They are usually prepared through ring opening of epoxides by using different azides in suitable solvents. The classical protocol uses[1a,b,2,3a] NaN_3 as reagent and NH_4Cl as coordinating salt in alcohol−water at 65−80 °C. Under these conditions, azidolysis is generally carried out over a long reaction time (12−48 h), and the azidohydrin is often accompanied by isomerization, epimerization, and rearrangement products.[1a,b]

The rate of reaction is not significantly improved by using NaN_3 in anhydrous CH_3CN in the presence of salts such as LiOTf[3a] or $Mg(ClO_4)_2$[3a] or by using Me_3SiN_3 with $Yb(Oi\text{-}Pr)_3$,[3b] $Ti(Oi\text{-}Pr)_4$,[3c,d] and $V(Oi\text{-}Pr)_3$[3e] in organic solvent. A good acceleration of the reaction is obtained by using Bu_3SnN_3,[3f] $SnCl_2{\cdot}2H_2O-Mg/NaN_3-H_2O/THF$,[3g] a recently reported system that permits working at room temperature, and titanium,[4a] aluminum,[4b] and tin[4c] azides in organic solvents. NaN_3 supported on porous solid acids (zeolite, alumina, and silica gel) has also been used;[4d] the rate of the reaction depends on the organic solvent used and on the amount of water impregnating the supports. High enantioselective azidolyses of meso epoxides have been achieved with Me_3SiN_3 in the presence of chromium (salen) complexes using ethereal solvents.[4e]

Azidolysis of unsymmetrical epoxides occurs with the attack of the azide ion on the less substituted carbon, except for the aryl-substituted epoxides.[1] Attempts to reverse the regioselectivity have had little success[3b,g,f,5a] with the exception of azidolysis that uses Et_3Al/HN_3 in dry toluene at −70 °C.[5b]

Table 1. Azidolysis by Sodium Azide of Epoxycyclohexane in Aqueous Medium



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entry	pH	salt	*T* (°C)	time (h)	products[a] (%) azido alcohol	diol
1	9.5		16	20	95	5
2	9.5		30	12	100[b]	
3	9.5	Yb(OTf)$_3$[c]	30	12	100	
4	9.5	$LiClO_4$[d]	30	6	100	
5	9.5	CTABr[e]	30	6	97	3
6	4.2[f]		16	1.2	92	8
7	4.2[f]		30	0.5	100[b]	
8	4.2[g]		30	4	100	
9	3.5[f]		30	0.5	87	13
10	2.5[g]		30	0.5	68	32

[a] GC ratios of the products.The epoxide conversion is quantitative. [b] 90% yield of isolated product. [c] 0.2 mol/equiv. [d] 5 mol/equiv; the starting pH was 8.4, and it was adjusted to 9.5 by adding NaOH. [e] 1 mol/equiv. [f] By using AcOH. [g] By using H_2SO_4.

Azidolysis of epoxides carried out in water only is a rarity.[1b,6]

Organic reactions in water have received much attention in the past decade.[7] Water is surprisingly amenable to many more types of reactions than chemists had once imagined and also offers economical advantages and cleaner chemical production methods.

We have performed aldol-like condensations[8] and oxidation[8] and cycloaddition reactions[9] in aqueous medium and have pointed out that the control of pH is crucial in order to obtain high yields and high selectivities.[10] In this paper, we report the azidolysis of epoxides **1**−**7** in water. The results show that both the reactivity and regioselectivity of the epoxide ring cleavage reaction in water and the competition of azido ion with the water or with hydroxide ion can be controlled by working at a suitable pH value.[11] Epoxycyclohexane (**1**) was chosen as a representative compound (Table 1). Azidolysis of **1** in aqueous 2.5 M NaN_3 (pH = 9.5) proceeded for 12 h at 30 °C and *trans*-azidohydrin was the sole reaction product that was isolated in pure form in 90% yield (Table 1,

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(1) (a) *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley: New York, 1971. (b) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297. (c) Coe, D. M.; Myers, P. L.; Parry, D. M.; Roberts, S. M.; Storer, R. *J. Chem. Soc., Chem. Commun.* **1990**, 151. (d) Jacobs, G. A.; Tino, J. A.; Zahler, R. *Tetrahedron Lett.* **1989**, *30*, 6955.

(2) (a) Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Eur. J. Org. Chem.* **1998**, *5*, 1675. (b) Nugent, T. C.; Hudlicky, T. *J. Org. Chem.* **1998**, *63*, 510. (c) Swift, G.; Swern, D. *J. Org. Chem.* **1967**, *32*, 511.

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(5) (a) Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1996**, *37*, 1675. (b) Mereyala, H. B.; Frei, B. *Helv. Chim. Acta* **1986**, *69*, 415.

(6) (a) Guy, A.; Doussot, J.; Garreau, R.; Godefroy-Falguieres, A. *Tetrahedron: Asymmetry* **1992**, *3*, 247. (b) DeMarinis, R. M.; Berchtold, G. A. *J. Am. Chem. Soc.* **1969**, *91*, 6525.

(7) (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: Glasgow, 1998. (b) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997.

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(11) (a) Blum[12a] carried out the azidolysis of benzanthracene oxides with NaN_3 in H_2O−acetone ca. 1:1.8, adjusting the pH of the mixture to 8 with H_2SO_4: (b) Recently, Whalen[12b] carefully studied the kinetics of aminolysis and azidolysis of benzo[*a*]pyrene diol epoxide in 1:9 dioxane/water at several pH values.

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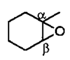
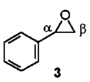
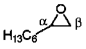
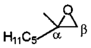
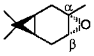
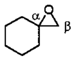
Table 2. Azidolysis by Sodium Azide of Epoxides in Aqueous Medium at 30 °C

Epoxide	pH	time (h)	regioselectivity (α/β attack)	products[a] (%)		yield[c] (%)
				azidoalcohols[b]	diol	
 **2**	9.5	12	35/65	100	-	50
	4.2[d]	0.5	79/21	100	-	65
	4.2[d,e]	1.5	78/22	75	25	
	4.2[f]	1.5	80/20	100	-	67
 **3**	9.5	13	97/3	100	-	90
	4.2[d]	0.3	97/3	100	-	92
 **4**	9.5	36	10/90	100[g]	-	
	9.5[h]	24	4/96	100	-	88
	4.2[d]	4	30/70	100	-	
 **5**	9.5[i]	27	20/80	85	15	
	9.5	120	20/80	86	14	
	9.5[h]	28	2/98	100	-	90
	4.2[d]	3	85/15	96	4	70
 **6**	9.5	144	35/65	100[j]	-	
	9.5[i]	60	35/65	100	-	55
	4.2[d]	48	86/14	92	8	70
	4.2[d, k]	5	75/25	90	10	
 **7**	9.5	20	3/97	88	12	77
	4.2[d]	1.5	70/30	94	6	58

[a] GC ratios of products. The epoxide conversion is quantitative if not otherwise specified. [b] α-azido-β-hydroxy + β-azido-α-hydroxy derivative. [c] Yield of main isolated product. [d] By using AcOH. [e] At 16 °C. [f] By using H_2SO_4. [g] Conversion 50%. [h] With CTABr, 1 mol/equiv. [i] At 100 °C. [j] Conversion 44%. [k] At 70 °C.

entry 2). At lower temperature, the nucleophilic attack of hydroxide ion was detectable, and 5% diol accompanied the azido alcohol (Table 1, entry 1). The presence of Yb(OTf)$_3$ did not affect the reaction rate, while $LiClO_4$ and cetyltrimethylammonium bromide (CTABr) accelerated azidolysis[13] (Table 1, entries 3–5). Under acidic conditions, the reaction was strongly accelerated. The best reaction conditions were pH 4.2 at 30 °C (Table 1, entry 7); at lower pH and temperature values there was competition from the nucleophilic attack of the water (Table 1, entries 6, 9, and 10). The use of acetic acid as acidifying agent was essential because it allowed the reaction to be performed in a buffered medium.[14] When H_2SO_4 was used, the starting pH 4.2 increased over time because the azido alcoholate consumed a proton equivalent, and the reaction rate slowed (Table 1, entry 8).

Table 2 illustrates the azidolysis of representative epoxides **2**–**7**.

At pH 9.5, the attack of azide ion preferentially occurred, as expected, on the less substituted β-carbon of all the epoxides with the exception of styrene oxide (**3**), in which the nucleophile predominantly attacked the more substituted benzylic α-carbon.[3g] ^{1}H and ^{13}C NMR data of the reaction products and a comparison with authentic samples indicate that the ring opening of **2** and **6** was diastereoselective, and *trans*-azidohydrins were the sole products.

Under acidic conditions (pH 4.2), compounds **2**, **5**, **6**, and **7** gave a reversed regioselectivity, while the attack of the azide ion on the more substituted α-carbon of 1,2-epoxyoctane (**4**) increased from 10% to 30%. No change of regioselectivity was observed in the azidolysis of **3**. Again, the ring opening of **2** and **6** was completely anti stereoselective. Thus, it was possible to change the regioselectivity in the azidolysis of α-disubstituted epoxides by simply working in aqueous medium and changing the reaction conditions from basic to acidic and or vice versa.

The 1,2-epoxy-2-methylheptane (**5**) and the azido alcohols from epoxide **5** and **6** are new compounds, and their structures are supported by ^{1}H and ^{13}C NMR data (see the Experimental Section) and previous work in this field.[15,16]

The regioselectivity under acidic conditions can be explained by considering that the attack of the azide ion on the more substituted α-carbon arises from the prior protonation of epoxide, which produces a considerably more positive charge on the tertiary α-carbon of **2**, **5**, **6**, and **7** than on the secondary β-carbon of **2** and **6** or the primary β-carbon of **5** and **7**. The α/β ratios of azidolyses of constitutional isomers **4** and **5** gave quantitative information about the protonation effect on the competitive attacks of secondary and tertiary carbon atoms compared with a primary carbon. The azide ion attack on secondary α-carbon of **4** at pH 4.2 and in the presence of CTABr is 11 times more favored than that observed in azidolysis carried out under basic conditions, while the nucleophilic attack on tertiary α-carbon of **5** under acidic conditions is 283 times more favored and causes an inversion of regioselectivity.

To our knowledge, this is the first reported investigation on the regioselectivity of azidolysis of epoxides carried out in aqueous acidic medium. The procedure is easy and is particularly useful for synthesizing tertiary azides that cannot be easily obtained by other methods. Thus, working under acidic conditions, the (+)-epoxycarane **6** is converted with good yield into the optically pure (−)-3β-azido-4α-hydroxy-*trans*-carane, which can then be easily reduced to the corresponding amino alcohol, which is a promising chiral auxiliary.

Reexamining the classical protocol for the azidolysis of unfunctionalized epoxides **1**–**4** and **7** reported in the literature[1b,2c,3a] and considering the results of this study, it is clear that in the classical method the reaction time is too long, the temperature is too high, and NH_4Cl and the alcoholic cosolvent are unnecessary. For example, the azidolysis of **2** in 8:1 methanol–water and in the presence of NH_4Cl (2.2 equiv) requires only 2 h at 80 °C and occurs

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(12) (a) Blum, J.; Ben-Shoshan, S. *J. Heterocycl. Chem.* **1983**, *20*, 1461. (b) Lin, B.; Islam, N.; Friedman, S.; Yagi, H.; Jerina, D. M.; Whalen, D. L. *J. Am. Chem. Soc.* **1998**, *120*, 4327.

(13) The reaction could occur in the pseudomicellar phase where the hydroxide counterion makes the pH higher than that of the aqueous phase.

(14) (a) The pK_a values of HN_3 and AcOH in water at 25 °C are 4.7 and 4.8, respectively.[1a,14b] A commercial buffered solution at pH 4.2 cannot be used because the addition of 5 mol/equiv of NaN_3 significantly increases the pH of the medium. (b) *Handbook of Chemistry and Physics*, 78th ed.; Lide, D. R., Ed.; CRC Press: New York, 1997–98; pp 8–45.

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in 12 h at room temperature, giving in all cases practically the same regioselectivity observed as when working in water only (12 h at room temperature, α/β = 35/65).

In 1989, we reported[15] that the epoxidation of alkenes could be carried out in water only by using peroxyacids. Coupling that procedure with the azidolysis here reported, it is possible to prepare azido alcohols from alkenes by a one-pot procedure. For example, the *trans*-2-azidocyclohexanol can be obtained in pure form from cyclohexene with 74% yield.

Experimental Section

General Procedures. All chemicals were purchased and used without any further purification. GC analyses were performed with an SPB-5 fused silica capillary column (30 m, 0.25 mm diameter), an "on column" injector system, an FID detector, and hydrogen as carrier gas. GC−MS analyses were carried out with 70 eV electron energy. Column chromatographies were carried out on silica gel (0.04−0.063 mm, 230−400 mesh ASTM). ^1H and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, respectively, in $CDCl_3$ as solvent and TMS as internal standard. pH measures were performed by using a combination refillable pH electrode. The azido alcohols from epoxides **1**,[3g] **2**,[3a,5b] **3**,[3a] **4**,[5d] and **7**[3a,5b] are known. The epoxide **5** and the azido alcohols from epoxides **5** and **6** are new compounds and are described below.

Azidolysis at pH = 9.5. Epoxide (5×10^{-3} mol) was added at the indicated temperature (Tables 1 and 2) to an aqueous solution of sodium azide (25×10^{-3} mol in 10 mL of water) and the heterogeneous mixture stirred for the time reported in Tables 1 and 2. The starting pH was 9.5, and it increased by 0.5−0.7 units during the reaction. The mixture was extracted with Et_2O (2 × 25 mL), saturated with NaCl, and extracted once again with Et_2O (25 mL). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the crude azido alcohol, which was purified by column chromatography (eluent *n*-hexanes−ethyl acetate 95:5). The reaction yield is reported in Tables 1 and 2. When the azidolysis was executed in the presence of salt, the molar ratio salt/epoxide indicated in Table 1 (see footnotes) was used.

Azidolysis at pH = 4.2. Epoxide (5×10^{-3} mol) was added at the indicated temperature (Tables 1 and 2) to an aqueous solution of sodium azide (25×10^{-3} mol in 8 mL of water and 4.6 mL of glacial acetic acid) and the heterogeneous mixture stirred for the time reported in Tables 1 and 2. The starting pH was 4.2, and it remained practically constant during the reaction. The mixture was extracted with Et_2O (2 × 25 mL), saturated with NaCl, and extracted once again with Et_2O (25 mL). The extracts were washed with 10% aqueous NaOH, dried (Na_2SO_4), and concentrated under reduced pressure to give the crude azido alcohol, which was purified by column chromatography (eluent *n*-hexanes−ethyl acetate 95:5). The reaction yield is reported in Tables 1 and 2.

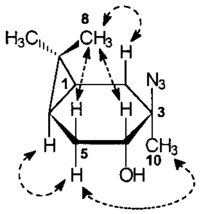
One-Pot Synthesis of *trans*-2-Azidocyclohexanol from Cyclohexene. Pure, powdered *m*-CPBA (2.2×10^{-3} mol) was added to a cold (1−3 °C), well-stirred suspension of cyclohexene (2.0×10^{-3} mol) in a 1 N solution of $NaHCO_3$ (12 mL) over a period of 3 min. The heterogeneous mixture was stirred for 40 min at room temperature. Powdered NaN_3 (9.0×10^{-3} mol) was then added, and the stirring was continued for 12 h at 30 °C. The mixture was then saturated (NaCl) and extracted with Et_2O (3 × 15 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure, furnishing 0.180 g of *trans*-2-azidocyclohexanol[3g] GC 98% pure, yield 74%.

1,2-Epoxy-2-methylheptane (5). Prepared in 94% yield by epoxidation with *m*-CPBA in water of 2-methyl-1-heptene:[15a] oil; ^1H NMR δ 0.84 (t, J = 6.7 Hz, 3H), 1.13−1.57 (m, 8H), 1.25 (s, 3H), 2.51 (d, J = 4.9 Hz, 1H), 2.55 (d, J = 4.9 Hz, 1H); ^{13}C NMR δ 13.9, 20.8, 22.5, 24.8, 31.8, 36.6, 53.8, 56.9. Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.82; H, 12.30.

1-Azido-2-hydroxy-2-methylheptane. Prepared in 90% yield, under basic conditions (pH 9.5, 28 h, 30 °C, CTABr 1 mol/equiv, Table 2 footnote h): oil; ^1H NMR δ 0.89 (t, J = 6.9 Hz, 3H), 1.17−1.56 (m, 8H), 1.19 (s, 3H), 2.01 (sb, 1H), 3.23 (d, J = 12.1 Hz, 1H), 3.28 (d, J = 12.1 Hz, 1H); ^{13}C NMR δ 13.9, 22.5, 23.3, 24.4, 32.2, 39.6, 60.8, 72.8. Anal. Calcd for $C_8H_{17}N_3O$: C, 56.11; H, 10.01; N, 24.54. Found: C, 56.20; H, 10.03; N, 24.51.

2-Azido-1-hydroxy-2-methylheptane. Prepared in 70% yield, under acidic conditions (pH 4.2, 3 h, 30 °C, Table 2, footnote d): oil; ^1H NMR δ 0.89 (t, J = 7.0 Hz, 3H), 1.17−1.56 (m, 8H), 1.26 (s, 3H), 2.11 (sb, 1H), 3.43 (d, J = 11.3 Hz, 1H), 3.49 (d, J = 11.3 Hz, 1H); ^{13}C NMR δ 13.9, 19.8, 22.5, 23.3, 32.1, 36.3, 65.1, 68.7. Anal. Calcd for $C_8H_{17}N_3O$: C, 56.11; H, 10.01; N, 24.54. Found: C, 56.22; H, 9.98; N, 24.61.

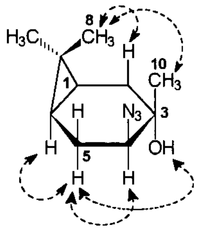
(−)-3*β*-Azido-4α-hydroxy-*trans*-carane. Prepared in 70% yield, under acidic conditions (pH 4.2, 48 h, 30 °C, Table 2, footnote d): mp 34−35 °C, from *n*-hexane−Et_2O; $[\alpha]_D$ −50.2° (c = 0.82, $CHCl_3$); ^1H NMR δ 0.69−0.80 (m, 2 H, 1-H, 6-H), 0.95 (s, 3 H, 8-CH_3), 1.00 (s, 3 H, 9-CH_3), 1.32 (dd, J = 14.6, 4.2 Hz, 1 H, 2-Hβ), 1.33 (s, 3 H, 10-CH_3), 1.68 (ddd, J = 14.6, 10.2, 7.8 Hz, 1 H, 5-Hα), 1.89 (sb, 1 H, 4-OH), 2.06 (dd, 1 H, J = 14.6, 7.3 Hz, 5-Hβ), 2.09 (dd, J = 14.6, 9.4 Hz, 1 H, 2-Hα), 3.34 (dd, J = 10.2, 7.3 Hz, 1 H, 4-H); ^{13}C NMR δ 15.0, 15.7, 18.0, 18.6, 20.8, 26.3, 28.5, 31.0, 65.3, 72.8. Anal. Calcd for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78;, N, 21.52. Found: C, 61.50; H, 8.75; N, 21.54.



Observed NOESY correlations

10-CH_3 / 5-Hα	8-CH_3 / 2-Hβ
8-CH_3 / 5-Hβ	6-H / 5-Hα
8-CH_3 / 4-H	

(+)-4*β*-Azido-3α-hydroxy-*cis*-carane. Prepared in 55% yield, under basic conditions (pH 9.5, 60 h, 100 °C, Table 2, footnote i): oil; $[\alpha]_D$ = +146.6° (c = 1.22, $CHCl_3$); ^1H NMR δ 0.63 (ddd, J = 9.0, 8.8, 2.8 Hz, 1 H, 6-H), 0.70 (ddd, J = 9.2, 9.0, 6.0 Hz, 1 H, 1-H), 1.03 (s, 6 H, 8- CH_3, 9- CH_3), 1.25 (dd, J = 15.2, 6.0 Hz, 1 H, 2-Hβ), 1.21 (s, 3 H, 10- CH_3), 1.60 (ddd, J = 16.1, 3.2, 2.8 Hz, 1 H, 5-Hβ), 1.78 (ddd, J = 15.2, 9.2, 1.4 Hz, 1 H, 2-Hα), 2.07 (sb, 1 H, 3-OH), 2.38 (ddd, J = 16.1, 8.8, 7.7 Hz, 1 H, 5-Hα), 3.39 (ddd, J = 7.7, 3.2, 1.4 Hz, 1 H, 4-H); ^{13}C NMR δ 14.9, 17.2, 17.3, 18.2, 22.0, 25.9, 28.5, 28.6, 63.9, 70.5. Anal. Calcd for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.55; H, 8.73; N, 21.58.



Observed NOESY correlations

10-CH_3 / 8-CH_3	5-Hα / 4-H
8-CH_3 / 2-Hβ	5-Hα / 3-OH
6-H / 5-Hα	

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