Efficient Regioselective Opening of Epoxides by Nucleophiles in Water under Simultaneous Ultrasound/Microwave Irradiation

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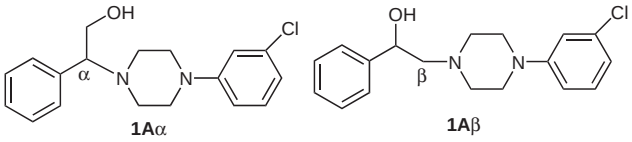
Abstract: Epoxide cleavage by nucleophiles in aqueous media may suffer from competition by water itself, yielding the diol as byproduct. However, when the reaction was carried out under high-intensity ultrasound or microwaves, attack by the nucleophile was strongly promoted and water no longer reacted. Best results were achieved under simultaneous ultrasound/microwave irradiation: a series of mono-, di- and trisubstituted oxiranes reacted rapidly with sodium azide or 1-(3-chlorophenyl)piperazine, usually leading to the corresponding more substituted alcohols in acceptable to high yields. This catalyst-free, greener protocol achieves a much faster cleavage of epoxides with a high regioselectivity.

Key words: epoxide opening, ultrasound, microwave, reaction in water, one-pot reaction

Epoxides are widespread in nature, standing at crossroads of several metabolic pathways; they also are useful building blocks for organic syntheses. Ring opening of epoxides by nucleophiles is one of the most versatile reactions among 'click chemistry' protocols, that often feature water as the solvent of choice.[1] The reaction with amines affords β-amino alcohols, important intermediates for carbohydrate and nucleoside synthesis.[2] It usually requires long reaction times and the use of a metal catalyst (e.g., Cu, Al, Sn, or Bi triflates, $ZrCl_4$).[3] An alternative route to the same products is the azidolysis of epoxides followed by reduction; side products, however, are often formed by this procedure and reaction times are not much shorter. In aqueous media competition between N_3^- and water is pH- and temperature-dependent, as is the regioselectivity.[4] Microwave-assisted cleavage of epoxides by amines is described in the literature, however, the metal catalyst was required in all reported instances.[5]

Aiming to develop an efficient, greener protocol for the regioselective opening of epoxides by nucleophiles, we studied the catalyst-free reaction in water under high-intensity ultrasound (US), microwaves (MW) and simultaneous US/MW irradiation.[6] We found that these means of physical activation induced a regioselectivity that was the reverse of that observed by Fringuelli et al., working at acidic pH under conventional conditions.[4]

We reacted a series of commercially available oxiranes with different degrees of substitution [2-phenyloxirane, *N*-(2,3-epoxypropyl)phthalimide, 1,2-epoxyoctane, cyclohexene oxide, (+)-limonene 1,2-epoxide] with sodium azide (A, Table 1) and 1-(3-chlorophenyl)piperazine[7] (B, Table 1) in water at neutral pH, without any metal catalyst added. We compared four different methods: 1) conventional heating at 50 °C under high-speed magnetic stirring (24–36 h), i.e. the typical 'on water' conditions described by Sharpless; 2) under MW irradiation (open vessel, 100 W, at 50 °C) in a multimode professional oven (Microsynth, Milestone); 3) under US (20.3 kHz, 70 W at 45 °C), using a titanium probe;[8] 4) under simultaneous US/MW irradiation (at 45 °C),[9] achieved by introducing in the same MW oven a probe equipped with a horn made of PEEK®.[10] Both US and MW dramatically accelerated the reaction, that went to completion in 0.5–2 hours whereas it took at least one day under stirring and conventional heating. Products were readily isolated by silica gel column chromatography after evaporation of the solvent. Results are gathered in Table 1. Reactions carried out under these conditions are completely *anti* stereoselective, as shown by the exclusive formation of the *anti* products in reactions of cyclic epoxides (entries 4, 5; Table 1). As regards the regiochemistry of ring opening for unsymmetrical epoxides (entries 2, 3, 5), reactions are regioselective, the attack of the N-nucleophiles (A, B) taking place on the less hindered epoxide carbon (β), except for 2-phenyloxirane (entry 1). The reverse regioselectivity observed for 1A,B is typical of benzylic substrates in accordance with the soft-base properties[11] of our nucleophiles (Figure 1).



1Aα **1A**β

Figure 1 Regioisomers from the reaction of 2-phenyloxirane with 1-(3-chlorophenyl)piperazine

Under nonconventional conditions (procedures 2–4), competition between water and the nucleophile did not occur; as shown in Table 1, the diol was never detected. On the contrary, reactions carried out under conventional heating were prone to nucleophilic attack by water, although Saidi et al. did not isolate the diols in the aminolysis of epoxides in water.[12] Trisubstituted oxiranes showed a modest reactivity. Under conventional heating

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(+)-(1*R*,2*S*,4*R*)-*cis*-limonene 1,2-epoxide (entry 5),[13] gave exclusively the *trans*-diaxial diol when reacted with 1-(3-chlorophenyl) piperazine, while its azidolysis exclusively led to azidohydrin **5Bβ**, albeit in low yields. Combined US/MW irradiation markedly improved yields (51% unoptimized yields) and cut down reaction times.

Table 1 Reaction Times and Yields for Epoxide Opening by Methods 1–4[14]

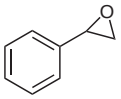
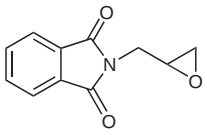
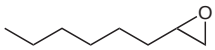
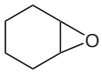
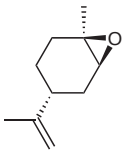
Entry	Epoxide	Nu[a]	Method	Time (h)	Selectivity α/β/diol[b] (isolated yields, %)	Conversion (%)
1		A[15,16]	1. Oil bath	24	12:19:29	60
			2. MW	2	16:20:0	36
			3. US	2	25:45:0	70
			4. US/MW	0.5	28:61:0	89
		B	1. Oil bath	24	88:0:0	88
			2. MW	1	90:0:0	90
			3. US	0.5	91:0:0	91
			4. US/MW	0.5	95:0:0	95
2[c]		A[17]	1. Oil bath	24	0:24:55	79
			2. MW	1	0:78:0	78
			3. US	1	0:80:0	80
			4. US/MW	1	0:86:0	86
		B	1. Oil bath	24	0:25:0	25
			2. MW	0.5	0:34:0	34
			3. US	0.5	0:40:0	40
			4. US/MW	0.5	0:61:0	61
3		A[18]	1. Oil bath	30	0:20:51	71
			2. MW	1.5	0:40:0	40
			3. US	1.5	0:43:0	43
			4. US/MW	1.5	0:59:0	59
		B	1. Oil bath	30	0:35:13	48
			2. MW	1.5	0:55:0	55
			3. US	1.5	0:61:0	61
			4. US/MW	1.5	0:79:0	79
4		A[19]	1. Oil bath	30	10:31	41
			2. MW	1.5	26:0	26
			3. US	1.5	30:0	30
			4. US/MW	1.5	56:0	56
		B	1. Oil bath	36	25:0	25
			2. MW	0.5	27:0	27
			3. US	0.5	32:0	32
			4. US/MW	0.5	50:0	50

Table 1 Reaction Times and Yields for Epoxide Opening by Methods 1–4[14] (continued)

Entry	Epoxide	Nu[a]	Method	Time (h)	Selectivity α/β/diol[b] (isolated yields, %)	Conversion (%)
5		A[20]	1. Oil bath	30	0:0:35	35
			2. MW	2.5	n.d.	<3
			3. US	3	n.d.	<3
			4. US/MW	2	0:39:0	39
		B[21]	1. Oil bath	30	0:20:0	20
			2. MW	2	0:11:0	11
			3. US	2	0:15:0	15
			4. US/MW	1.5	0:51:0	51

[a] Nucleophiles: A = 1-(3-chlorophenyl)piperazine, B = sodium azide.
[b] α: Less-substituted alcohol, β: more-substituted alcohol.
[c] The amount of 0.8 mL of $BMIMBF_4$ (3-butyl-1-methylimidazolium tetrafluoroborate) was added as a co-solvent.

By applying a combination of 1D and 2D NMR experiments (i.e., ^1H–^{13}C HMQC, ^1H–^1H COSY and ^1H–^1H NOESY) we were able to unambiguously determine the 1*R*,2*R*,4*R* stereochemistry of **5Bβ** (Figure 2).

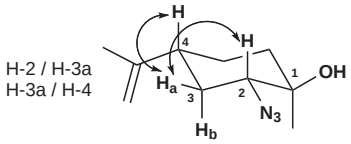
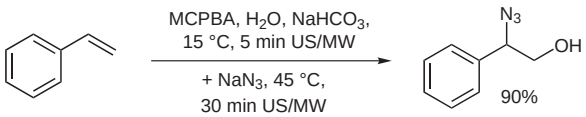


Figure 2 NOE correlations for **5Bβ**

Efficient cooling by circulation of a refrigerated fluid that was inert to MW ensured temperature control, a crucial feature when working in water under combined US/MW irradiation. The device illustrated in Figure 3 made the one-pot alkene → epoxide → azide reaction sequence feasible. Scheme 1 shows the preparation of 2-azido-2-phenylethanol from styrene; sodium azide was added after five minutes US/MW irradiation at 15 °C.

Figure 3 Typical setup for US/MW irradiation, showing the cooling system



Scheme 1 Scheme of the one-pot reaction

In conclusion, here we disclose an efficient, catalyst-free synthetic procedure for a regioselective opening of epoxides by some N-nucleophiles in water. This result was achieved under US or MW irradiation, or, better still, under simultaneous US/MW irradiation that strongly accelerated the cleavage with a high regioselectivity. Interestingly, 2-azido-2-phenylethanol was prepared in a one-pot manner in high yield from styrene.

Acknowledgment

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(14) **General Procedure**
In a 50 mL two-necked round-bottomed flask (equipped with an optical-fiber thermometer for reactions under MW or combined US/MW) the epoxide (2.5 mmol), the amine (or NaN_3, 2.5 mmol), and H_2O (15 mL) were mixed and subjected to procedures 1–4.
(15) 2-[4-(3-Chlorophenyl)piperazin-1-yl]-2-phenylethanol (**1Aα**): pale yellow oil; R_f = 0.56 ($CHCl_3$–MeOH, 19:1). IR (film): 3584, 1595, 1452, 1238, 1028, 954, 765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.22 (m, 5 H, H-2′, -3′, -4′, -5′, -6′), 7.14 (t, *J* = 8.1 Hz, 1 H, H-5‴), 6.83–6.72 (m, 3 H, H-2‴, -4‴, -6‴), 4.03 (m, 1 H, H-2), 3.74 (m, 2 H, H-2, -3), 3.20 (m, 4 H, H-3″a,b, H-5″a,b), 2.74–2.54 (m, 4 H, H-2″a,b, H-6″a,b). MS (CI, isobutane): *m/z* = 317 $[MH]^+$.
(16) 2-[4-(3-Chlorophenyl)piperazin-1-yl]-1-phenylethanol (**1Aβ**): pale yellow oil; R_f = 0.43 ($CHCl_3$–MeOH, 19:1). IR (film): 3400, 1595, 1566, 1481, 1244, 1057, 947, 777 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.38 (m, 5 H, H-2′, -3′, -4′, -5′, -6′), 7.22 (t, *J* = 8.1 Hz, 1 H, H-5‴), 6.94–6.83 (m, 2 H, H-2‴, -4‴, -6‴), 4.86 (m, 1 H, H-1), 3.31 (m, 4 H, H-3″a,b, H-5″a,b), 2.95–2.92 (m, 2 H, H-2″a,b), 2.70–2.56 (m, 4 H, H-2, -3, H-6″a,b). MS (CI, isobutane): *m/z* = 317 $[MH]^+$.
(17) 2-{3-[4-(3-Chlorophenyl)piperazin-1-yl]-2-hydroxypropyl} isoindoline-1,3-dione (**2Aβ**): pale yellow oil; R_f = 0.39 ($CHCl_3$–MeOH, 19:1). IR (film): 3327, 1626, 1576, 1437, 1244, 893 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.87–7.81 (m, 4 H, H-3, -4, -5, -6,), 7.17 (m, 1 H, H-5‴), 6.80–6.65 (m, 3 H, H-2‴, -4‴, -6‴), 4.21 (m, 1 H, H-2′), 3.50 (m, 2 H, H-1′a,b), 2.57 (m, 2 H, H-3′a,b), 2.90–2.40 (m, 8 H, H-2″a,b, H-3″a,b, H-5″a,b, H-6″a,b). MS (CI, isobutane): *m/z* = 400 $[MH]^+$.
(18) 1-[4-(3-Chlorophenyl)piperazin-1-yl]octan-2-ol (**3Aβ**): pale yellow oil; R_f = 0.40 (hexane–EtOAc, 7:3). IR (film): 3460, 1595, 1487, 1234, 1153, 987, 837, 769 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.10 (t, *J* = 8.1 Hz, 1 H, H-2″), 6.85–6.50 (m, 3 H, H-4″, -5″, -6″), 3.70 (m, 1 H, H-2), 3.10 (m, 4 H, H-3′a,b, H-5′a,b), 2.75 (m, 2 H, H-2′a,b), 2.50 (m, 2 H, H-6′a,b), 2.30 (m, 2 H, H-1a,b), 1.50–1.00 (m, 10 H, H-3a,b, H-4a,b, H-5a,b, H-6a,b, H-7a,b), 0.95 (br s, 3 H, CH_3). MS (CI, isobutane): *m/z* = 325 $[MH]^+$.
(19) *trans*-2-[4-(3-Chlorophenyl)piperazin-1-yl]cyclohexanol (**4A**): pale yellow oil; R_f = 0.13 (PE–EtOAc, 8:2). IR (film): 3462, 1597, 1495, 1263, 1105, 1014, 954, 771, 681 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.02–6.77 (m, 4 H, H-2″, -4″, -5″, -6″), 4.16 (m, 1 H, H-1), 3.43 (m, 1 H, H-2), 3.23–3.19 (m, 4 H, H-3′a,b, H-5′a,b), 2.88 (m, 2 H, H-2′a,b), 2.58 (m, 2 H, H-5′a,b), 2.40–1.15 (m, 8 H, H-3,a,b, H-4a,b, H-5a,b, H-6a,b). MS (CI, isobutane): *m/z* = 295 $[MH]^+$.
(20) (1*R*,2*R*)-2-[4-(3-Chlorophenyl)piperazin-1-yl]-1-methyl-4-(prop-1-en-2-yl)cyclohexanol (**5Aβ**): pale yellow oil; R_f = 0.62 (hexane–EtOAc, 7:3). IR (film): 3462, 2361, 1595, 1450, 1238, 1126, 987, 767 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.17 (t, *J* = 8.1 Hz, 1 H, H-2‴), 6.87 (m, 3 H, H-4, -5, -6), 4.96 (m, 1 H, H-9a), 4.87 (m, 1 H, H-9b), 3.47 (m, 1 H, H-2), 3.22 (m, 4 H, H-3″a,b, H-5″a,b), 2.90 (m, 2 H, H-2″a,b), 2.68 (m, 2 H, H6″a,b), 2.5 (br s, 1 H, OH). MS (CI, isobutane): *m/z* = 349 $[MH]^+$.
(21) (1*R*,2*R*,4*R*)-2-Azido-1-methyl-4-(prop-1-en-2-yl)cyclohexanol (**5Bβ**): colorless oil; R_f = 0.24 ($CHCl_3$–MeOH, 19:1). IR (film): 3450, 2094, 1645, 1454, 1261, 1032, 891 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.8 (m, 2 H, H-9a,b), 3.55 (br s, 1 H, H-2), 2.20 (m, 1 H, H-4), 2.00 (m, 1 H, H-3a), 1.85 (m, 1 H, H-3b), 1.73 (m, 3 H, H-10, CH_3), 1.45 (br s, 1 H, OH), 1.40 (m, 3 H, H-7, CH_3). MS (CI, isobutane): *m/z* = 196 $[MH]^+$.