

## Regioselective Ring Opening of Epoxides with Lithium Azide

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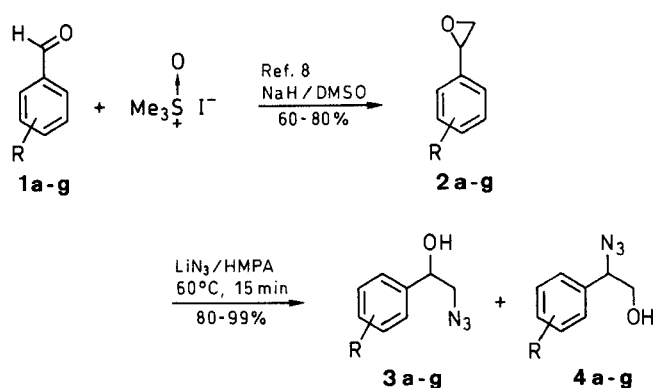
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Regioselective ring opening of substituted phenyloxirane was achieved with lithium azide/hexamethylphosphoramide by attack of azide at the non-benzylic position of the epoxide, leading to 1-aryl-2-azidoethanol.

The opening of the oxirane ring by an alkali azide is a straightforward route to vicinal azido alcohols which are the precursors of  $\beta$ -amino alcohols.<sup>1</sup> The increasing availability of nonfunctionalized chiral epoxides<sup>2</sup> makes them powerful intermediates in the synthesis of optically pure amino alcohols. However the regioselectivity of the nucleophilic opening is thoroughly dependent on the mechanism of the reaction and particularly on steric and electronic factors<sup>3</sup>. With aryloxirane,  $\pi$ -conjugating groups tend to favor attack at C<sub>2</sub> and with good  $\pi$ -donors substituents, stabilization of the incipient carbocation in benzylic position offsets steric hindrance,<sup>4</sup> except for a few exceptions where an inverted regioselectivity is observed.<sup>5</sup> Recently, in an attempt to prepare 2-azido-1-phenylethanol (**3**) for enzymatic kinetic resolution, all the attempts to open styrene oxide by azide regardless of the reaction conditions employed, failed and gave the regioisomer **4** with the azido group at the benzylic position.<sup>6</sup> We have recently reported some preliminary results on a mild procedure for the regio- and stereoselective ring opening of phenyloxirane at the non-benzylic position by lithium azide in hexamethylphosphoramide (HMPA).<sup>7</sup> The present paper describes the application of this methodology to electron-rich substituted aromatic epoxides **2** which are precursors of catecholamines and related compounds. Aromatic epoxides are easily obtained from

corresponding benzaldehydes following the classical Corey procedure<sup>8</sup> (Table 1). As shown in the Table 2 the regioselectivity of the nucleophilic attack is not affected by the increasing of the electronic density of the aromatic nucleus. In all cases the S<sub>N</sub>2 mechanism in the ring opening is largely favored in the experimental conditions examined. No longer reaction times were required for these epoxides possessing electron-donating substituents as would be expected from the reduced electrophilic



1-4	R	1-4	R
<b>a</b>	2-MeO	<b>e</b>	2,3-(MeO) <sub>2</sub>
<b>b</b>	4-MeO	<b>f</b>	2,4-(MeO) <sub>2</sub>
<b>c</b>	4-Me	<b>g</b>	2,5-(MeO) <sub>2</sub>
<b>d</b>	2-Me		

Table 1. Epoxides **2** Prepared

Prod-uct	Yield <sup>a</sup> (%)	bp (°C)/Torr	n <sub>D</sub> <sup>20</sup>	<sup>1</sup> H NMR <sup>b</sup> (CDCl <sub>3</sub> /TMS) $\delta$ , <i>J</i> (Hz) 200 MHz	<sup>13</sup> C NMR <sup>b</sup> (CDCl <sub>3</sub> /TMS) $\delta$
<b>2a</b>	75	125/0.25	1.5400	2.73 (1H, dd, <i>J</i> = 5.7, 2.7), 3.15 (1H, dd, <i>J</i> = 5.7, 4.1), 3.88 (3H, s), 4.23 (1H, dd, <i>J</i> = 4.1, 2.7), 6.89–7.18 (4H, m)	48.1 (C-2), 50.5 (C-1), 55.3 (OMe), 110.0, 120.6, 124.9, 126.0, 128.7, 158.0 (C <sub>6</sub> H <sub>4</sub> )
<b>2b</b>	75	120/0.25	1.5410	2.82 (1H, d, <i>J</i> = 5.3, 2.6), 3.13 (1H, dd, <i>J</i> = 5.3, 4.0), 3.81 (4H, m), 6.89, 7.21 (4H, AB pattern, <i>J</i> = 8.8)	50.9 (C-2), 52.1 (C-1), 55.2 (OMe), 113.9, 126.7, 129.3, 159.6 (C <sub>6</sub> H <sub>4</sub> )
<b>2c</b>	80	170/18	1.5250	2.38 (3H, s), 2.84 (1H, dd, <i>J</i> = 5.5, 2.6), 3.13 (1H, dd, <i>J</i> = 5.5, 4.1), 3.86 (1H, dd, <i>J</i> = 4.1, 2.6), 7.19 (4H, s)	21.0 (Me), 51.9 (C-1), 52.2 (C-2), 125.3, 129.1, 134.4, 137.8 (C <sub>6</sub> H <sub>4</sub> )
<b>2d</b>	61	145/0.25	1.5295	2.47 (3H, s), 2.72 (1H, dd, <i>J</i> = 5.7, 2.7), 3.19 (1H, dd, <i>J</i> = 5.7, 4.1), 4.04 (1H, dd, <i>J</i> = 4.1, 2.7), 7.26 (4H, m)	18.7 (Me), 50.1 (C-1), 50.4 (C-2), 124.1, 126.1, 127.7, 129.8, 135.9, 136.1 (C <sub>6</sub> H <sub>4</sub> )
<b>2e</b>	65	195/18	1.5345	2.72 (1H, dd, <i>J</i> = 5.7, 2.6), 3.14 (1H, dd, <i>J</i> = 5.7, 4.2), 3.85 (3H, s), 3.87 (3H, s), 4.20 (1H, dd, <i>J</i> = 4.2, 2.6), 6.69 (1H, dd, <i>J</i> = 7.7, 1.5), 6.73 (1H, dd, <i>J</i> = 8.1, 1.5), 6.99 (1H, d, <i>J</i> = 7.9)	47.9 (C-2), 50.4 (C-1), 55.6 (OMe), 60.9 (OMe), 111.7, 116.4, 124.2, 131.4, 147.9, 152.3 (C <sub>6</sub> H <sub>3</sub> )
<b>2f</b>	75	170/0.25	1.5395	2.66 (1H, dd, <i>J</i> = 5.8, 2.6), 3.12 (1H, dd, <i>J</i> = 5.8, 4.1), 3.73 (3H, s), 3.80 (3H, s), 4.19 (1H, dd, <i>J</i> = 4.1, 2.6), 6.77 (3H, m)	47.9 (C-2), 50.5 (C-1), 55.4 (OMe), 55.8 (OMe), 110.2, 111.2, 113.3, 127.0, 152.1, 153.7 (C <sub>6</sub> H <sub>3</sub> )
<b>2g</b>	60	175/0.25	1.5345	2.68 (1H, dd, <i>J</i> = 5.8, 2.6), 3.11 (1H, dd, <i>J</i> = 5.8, 4.1), 3.73 (3H, s), 3.80 (3H, s), 4.18 (1H, dd, <i>J</i> = 4.1, 2.6), 6.78 (3H, m)	48.0 (C-2), 50.6 (C-1), 55.5 (OMe), 55.8 (OMe), 110.3, 111.3, 113.4, 127.1, 152.1, 153.8 (C <sub>6</sub> H <sub>3</sub> )

<sup>a</sup> Yield of isolated pure product in NMR.

<sup>b</sup> Recorded on a Bruker AC 200 spectrometer.

<sup>c</sup> Analytical data are in accordance with those given in the literature.<sup>9</sup>

**Table 2.** Reaction of Epoxides **2** with Lithium Azide

Educt	Yield (%) <sup>a, b</sup>	Ratio <sup>c</sup> 3/4	Molecular Formula <sup>d</sup>	Prod-uct	IR $\nu$ (cm <sup>-1</sup> )	<sup>1</sup> H NMR (CDCl <sub>3</sub> /TMS) $\delta$ , <i>J</i> (Hz) 200 MHz	<sup>13</sup> C NMR (CDCl <sub>3</sub> /TMS) $\delta$
<b>2a</b>	81 (52)	99:1	C <sub>9</sub> H <sub>11</sub> O <sub>2</sub> N <sub>3</sub> (193.2)	<b>3a</b>	(CCl <sub>4</sub> ) 3600–2100	2.95 (1H, br s), 3.48 (2H, m), 3.85 (3H, s), 5.11 (1H, m), 6.89 (1H, dd, <i>J</i> = 8.2, 1.0), 7.00 (1H, td, <i>J</i> = 7.5, 1.1), 7.35 (2H, m)	55.2 (OMe), 56.3 (C-1), 69.8 (C-2), 110.3, 120.8, 126.9, 128.3, 129.0, 156.0 (C <sub>6</sub> H <sub>4</sub> )
<b>2b</b>	98 (60)	80:20	C <sub>9</sub> H <sub>11</sub> O <sub>2</sub> N <sub>3</sub> (193.2)	<b>3b</b>	(CH <sub>2</sub> Cl <sub>2</sub> ) (3560–2095)	2.75 (1H, br s), 3.40 (2H, ABX, <i>J</i> <sub>AB</sub> = 12.5, <i>J</i> <sub>AX</sub> = 8.8 Hz, <i>J</i> <sub>BX</sub> = 3.4), 3.80 (3H, s), 4.80 (1H, dd, <i>J</i> <sub>AX</sub> = 8.8, <i>J</i> <sub>BX</sub> = 3.4), 6.89 (AB, 2H, d, <i>J</i> = 8.4), 7.29 (AB, 2H, d, <i>J</i> = 8.4)	55.2 (OMe), 57.8 (C-1), 72.8 (C-2), 113.9, 127.1, 132.7, 159.4 (C <sub>6</sub> H <sub>4</sub> )
				<b>4b</b>	(CH <sub>2</sub> Cl <sub>2</sub> ) 3560–2100	2.30 (1H, br s), 3.70 (2H, d, <i>J</i> = 6.5), 3.80 (3H, s), 4.60 (1H, t, <i>J</i> = 6.5), 6.88 (AB, 2H, d, <i>J</i> = 8.3), 7.24 (AB, 2H, d, <i>J</i> = 8.4)	55.2 (OMe), 66.2 (C-1), 67.2 (C-2), 114.2, 128.1, 128.3, 159.7 (C <sub>6</sub> H <sub>4</sub> )
<b>2c</b>	98 (56)	88:12	C <sub>9</sub> H <sub>11</sub> ON <sub>3</sub> (177.2)	<b>3c</b>	(CCl <sub>4</sub> ) 3400–2120	2.37 (3H, s), 2.65 (1H, br s), 3.42 (2H, ABX, <i>J</i> <sub>AB</sub> = 12.5, <i>J</i> <sub>AX</sub> = 8.3, <i>J</i> <sub>BX</sub> = 3.7), 4.83 (1H, d, <i>J</i> <sub>AX</sub> = 8.3, <i>J</i> <sub>BX</sub> = 3.7), 7.17–7.28 (4H, m)	21.0 (Me), 57.9 (C-1), 73.1 (C-2), 125.8, 129.3, 137.5, 138.0 (C <sub>6</sub> H <sub>4</sub> )
				<b>4c</b>	(CCl <sub>4</sub> ) 3600–2120	2.0 (1H, br s), 2.37 (3H, s), 3.73 (2H, d, <i>J</i> = 6.5), 4.65 (1H, t, <i>J</i> = 6.5), 7.25 (4H, m)	21.0 (Me), 66.3 (C-1), 67.6 (C-2), 127.0, 129.5, 133.0, 138.5 (C <sub>6</sub> H <sub>4</sub> )
<b>2d</b>	99 (75)	86:14	C <sub>9</sub> H <sub>11</sub> ON <sub>3</sub> (177.2)	<b>3d</b>	(CCl <sub>4</sub> ) 3500–2100	2.33 (3H, s), 2.75 (1H, br s), 3.38 (2H, m), 5.07 (1H, m), 7.19–7.28 (3H, m), 7.49 (1H, m)	18.8 (Me), 56.8 (C-1), 69.9 (C-2), 125.4, 126.4, 128.0, 130.4, 134.4, 138.5 (C <sub>6</sub> H <sub>4</sub> )
				<b>4d</b>	(CCl <sub>4</sub> ) 3500–2100	2.10 (1H, br s), 2.40 (3H, s), 3.73 (2H, d, <i>J</i> = 6.5), 4.95 (1H, t, <i>J</i> = 6.5), 7.23–7.28 (4H, m)	19.1 (Me), 64.4 (C-2), 65.6 (C-1), 126.5, 128.3, 130.8, 134.2, 135.6 (C <sub>6</sub> H <sub>4</sub> )
<b>2e</b>	98 (75)	80:20	C <sub>10</sub> H <sub>13</sub> O <sub>3</sub> N <sub>3</sub> (223.2)	<b>3e</b>	(CCl <sub>4</sub> ) 3620–2120	3.0 (1H, br s), 3.42 (2H, m), 3.86 (6H, s), 5.12 (1H, br t), 6.90–7.07 (3H, m)	55.8 (OMe), 57.2 (C-1), 60.8 (C-2), 69.3 (OMe), 112.2, 118.6, 124.3, 133.9, 145.9, 152.4 (C <sub>6</sub> H <sub>3</sub> )
				<b>4e</b>	(CCl <sub>4</sub> ) 3500–2120	2.05 (1H, br s), 3.73 (2H, m), 3.88 (6H, s), 5.10 (1H, m), 6.88–6.96 (2H, m), 7.08 (1H, d, <i>J</i> = 8)	55.7 (OMe), 61.2 (C-2), 62.2 (OMe), 65.7 (C-1), 112.6, 119.2, 124.5, 129.9, 146.7, 152.7 (C <sub>6</sub> H <sub>3</sub> )
<b>2f</b>	99 (53)	99:1	C <sub>10</sub> H <sub>13</sub> O <sub>3</sub> N <sub>3</sub> (223.2)	<b>3f</b>	(CCl <sub>4</sub> ) 3600–2120	2.90 (1H, br s), 3.47 (2H, m), 3.78 (3H, s), 3.81 (3H, s), 5.10 (1H, m), 6.80 (2H, br s), 7.00 (1H, br s)	55.6 (OMe), 56.3 (C-1), 69.8 (C-2), 113.3, 112.9, 113.4, 129.4, 150.2, 153.7 (C <sub>6</sub> H <sub>3</sub> )
<b>2g</b>	98 (76)	99:1	C <sub>10</sub> H <sub>13</sub> O <sub>3</sub> N <sub>3</sub> (223.2)	<b>3g</b>	(CCl <sub>4</sub> ) 3590–2100	2.95 (1H, br s), 3.45 (2H, ABX, <i>J</i> <sub>AB</sub> = 12.5, <i>J</i> <sub>AX</sub> = 8.5, <i>J</i> <sub>BX</sub> = 3.4), 3.77 (3H, s), 3.80 (3H, s), 5.08 (2H, dd, <i>J</i> <sub>AX</sub> = 8.5, <i>J</i> <sub>BX</sub> = 3.4), 6.80 (2H, br s), 7.00 (1H, br s)	55.6 (OMe), 56.3 (C-1), 69.7 (C-2), 111.3, 112.9, 113.3, 129.4, 150.1, 153.7 (C <sub>6</sub> H <sub>3</sub> )

<sup>a</sup> Determined by NMR.<sup>b</sup> Yield of 1-aryl-2-azidoethanols **3** isolated by column chromatography in brackets.<sup>c</sup> 99:1 means that only one regioisomer could be detected.<sup>d</sup> Satisfactory microanalyses obtained: C ± 0.25, H ± 0.18, N ± 0.26.

character of the oxirane ring. This clearly shows the minor importance of the electronic factors as compared to the steric factor during this S<sub>N</sub>2 intermolecular process. In conclusion we have shown in this work that the ring-opening reaction of substituted phenyloxiranes **2** by lithium azide HMPA is regioselective and leads to 1-aryl-2-azidoethanols **3**. This method provides a useful synthesis of 2-amino-1-arylethanols which are of pharmacological interest.

#### 1-(2-Methoxyphenyl)-, (**3a**), and 2-(2-Methoxyphenyl)-1-azidoethanol (**4a**); Typical Procedure:

In a typical procedure, LiN<sub>3</sub> (0.06 g; 1.2 mmol) was added to a solution of (2-methoxyphenyl)oxirane (**2a**; 0.195 g; 1 mmol) in dry HMPA (1 mL). The suspension was stirred at 60°C during 18 h. After cooling, the yellow mixture obtained was poured into ice-water (10 mL) and then the mixture was extracted with Et<sub>2</sub>O. The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to afford 0.155 g (81 %) of a mixture of the two regioisomers which were separated by flash chromatography on silica gel (15–14 μm), with heptane/EtOAc (7:3) as the eluent.

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