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Rearrangement of (1,2,4-Triazol-4-yl)ethanols to (1,2,4-Triazol-1-yl)ethanols

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Abstract: The mechanism of rearrangement of β-hydroxyethyl-(1,2,4-triazoles) has been shown using crossover experiments to be intermolecular and free energy profiles show that reactions are thermodynamically-controlled.

Rees and coworkers showed that flash vacuum pyrolyses (650-800 °C) of phenyl-substituted triazoles caused fragmentation and aryl shifts.[1] In the condensed phase at 350 °C, 4-alkyl-3,5-diphenyl-1,2,4-triazoles rearrange to the corresponding 1-alkyl derivatives.[2,3] A similar 4- to 1-alkyl shift occurs in β-hydroxyethyl-(1,2,4-triazoles), e.g., **4** to **1** (Fig. 1), under basic conditions at temperatures below 200 °C.[4] We now report details of our recent mechanistic investigations of triazole tertiaryl alcohols,[5] which are of interest because they possess plant growth and fungicidal activities.[6]

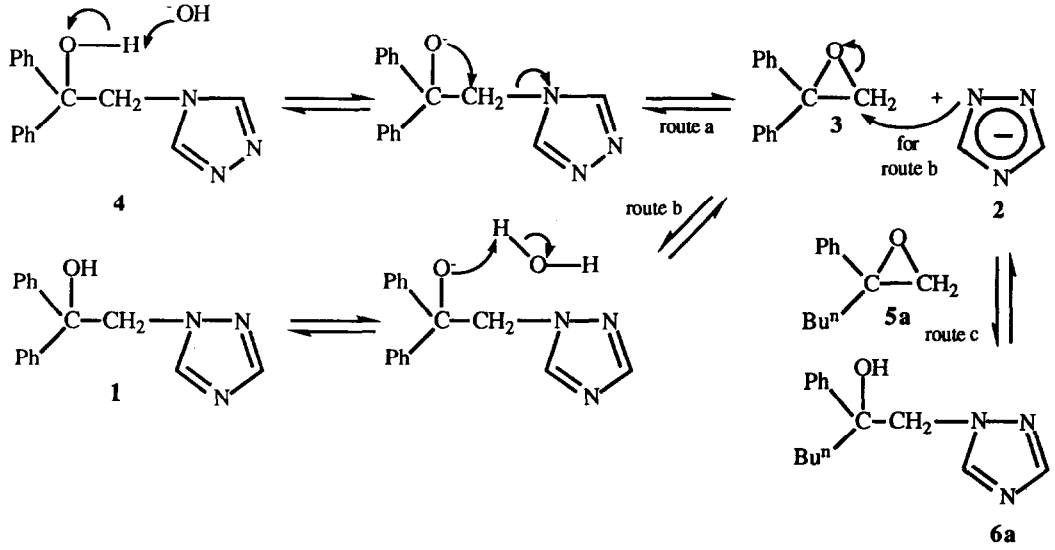


Figure 1. Formation of crossover product (**6a**) during isomerisation of 1,1-diphenyl-1-(1,2,4-triazol-4-yl)ethanol (**4**) to isomer (**1**)

The mechanism (Figure 1) proposed[5] for the rearrangement of 1,1-diphenyl-(1,2,4-triazol-4-yl) ethanol (**4**) to the corresponding 1-isomer (**1**) involves nucleophilic attack by the alkoxide of **1**, leading to the triazole anion (**2**) and 1,1-diphenyl epoxide (**3**); neighbouring group participation in this step accounts for the greater reactivity and hence lower temperatures for this rearrangement compared with the other examples.[1,2] When the epoxide (**3**) then reacts by the kinetically favoured route b (rather than the reverse reaction route a) the 1-isomer (**1**) is formed. In the presence of a second epoxide (e.g., 1-phenyl-1-butyl epoxide), the crossover product (**6a**) can be obtained, presumably *via* route c.

Two features of the mechanism (Figure 1) are: (i) nucleophilic displacement of the triazole anion and, (ii) reversibility of the reactions. To confirm these mechanistic proposals, we have constructed free energy profiles from the rates of decomposition of the triazole isomers **1** and **4**, and the product ratios for the reaction of the triazole anion with epoxides (Figure 2).

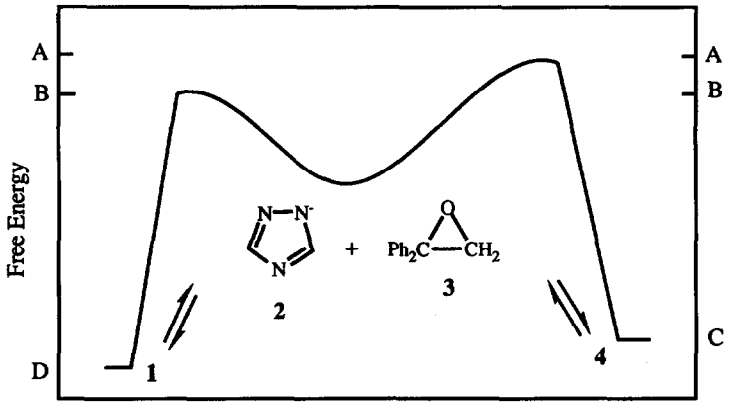


Figure 2. Free energy profile for the production of the alkoxide of 1-alkyl-1,2,4-triazole (**1**) from triazole anion (**2**) and epoxide (**3**), and from rearrangement of the alkoxide of 4-isomer (**4**).

RESULTS

The effect of substrate concentrations on the regioselectivity of the reaction of the triazole anion (**2**) with 1,1-diphenyl epoxide (**3**) in dimethylformamide (DMF) to give a mixture of **1** and **4** is shown in Table 1, and the effect of temperature for two substrate concentrations and two solvents is shown in Table 2.

First order rate constants were obtained for decomposition of the triazole isomers (**1** and **4** and **6** and **7**) in 0.1M solutions of N-methyl-2-pyrrolidinone (NMP), containing excess sodium hydroxide pellets. Typical kinetic data for 5M and 0.1M substrate concentrations in NMP are shown in Table 3 and for decompositions in polyethylene glycol 200 (PEG 200) are given in Table 4.

Table 1. Effect of Concentration on the Regioselectivity of Kinetically-Controlled Triazolisation of 1,1-Diphenyl epoxide (**3**) in Dimethylformamide at 86 °C to give **1** and **4**.

Concentration/M	1:4 Isomer Ratio	Concentration/M	1:4 Isomer Ratio
0.1	92:8	5.0	79:21
1.0	89:11	10.0	76:24
2.0	87:13	(Neat)	(70:30)

Table 2. Effect of Concentration and Temperature on the Regioselectivity of Kinetically-Controlled Triazolisation of 1,1-Diphenylepoxide (**3**) in Dimethylformamide and Polyethylene Glycol 200 to give **1** and **4**.

		Dimethylformamide		Polyethylene Glycol 200	
Concentration/M	Temperature/°C	Time/hr	1:4[a]	Time/hr	1:4
0.1	60	20	92:8	22	84:16
0.1	100	1.5	91:9	1.5	82:18
0.1	140	0.15	92.8[b]	0.13	81:19
0.01	60	20	95:5[b]	22	85:15
0.01	100	1.5	94:6[b]	1.5	84:16
0.01	140	0.13	93:7	0.13	84:16[b]

[a] Isomer ratios are the average of three independent measurements in agreement within ±1, except where stated otherwise.

[b] Duplicate measurement.

Table 3. Effect of Concentration and Temperature on the Rate Constants (k/s^{-1}) for Decomposition of Triazole Isomers (**1** and **4**) by Excess Sodium Hydroxide in N-methyl-2-pyrrolidinone.

	5M reactions			0.1M reactions	
Isomer	138 °C	150 °C	180 °C	133.8 °C	146.2 °C
1	6.18×10^{-8}	1.56×10^{-7}	4.91×10^{-7}	6.9×10^{-5}	1.23×10^{-4}
4	1.25×10^{-4}	6.10×10^{-4}	4.07×10^{-3}	6.18×10^{-4}	1.63×10^{-3}

Table 4. Effect of Concentration on the Rate Constants (k/s^{-1}) and Activation Parameters for Decomposition of Triazole Isomers **1** and **4** by Excess Sodium Hydroxide in Polyethylene Glycol 200 at 149.8 °C.

Isomer	0.1M	0.01M	(135.6 °C)	$\Delta H^{\neq}$ kcal mol^{-1}	$\Delta S^{\neq}$ cal mol^{-1} K^{-1}
1	$(1.4 \pm 0.1) \times 10^{-5}$	$(2.06 \pm 0.05) \times 10^{-5}$	(4.17×10^{-6})	38 ± 3	8 ± 6
4	$(1.8 \pm 0.3) \times 10^{-4}$	$(1.93 \pm 0.01) \times 10^{-4}$	(4.07×10^{-5})	37 ± 2	10 ± 5

Table 5. Free Energy Profile (kcal mol^{-1}) for Isomerisations of Triazole Isomers **1** and **4**, and (**6** and **7**) 0.1M in N-methyl-2-pyrrolidinone

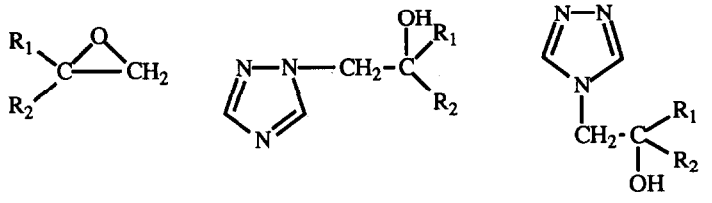
Substrate	Temp/°C	AB[a]	BD	AC	CD (calc)[b]	CD (obs)[c]
1, 4	150	2.31	32.48	30.23	4.56 ± 0.44[d]	4.17 ± 0.13
6a, 7a	135.4	2.31	32.65	30.64	4.32 ± 0.37	4.45 ± 0.15
6b, 7b	135.5	2.19	32.48	30.71	3.96 ± 0.33	4.05 ± 0.12
6c, 7c	135.5	2.16	33.41	31.52	4.05 ± 0.32	4.45 ± 0.15
6d, 7d	135.5	2.17	33.46	31.47	4.16 ± 0.26	4.30 ± 0.15

[a] Calculated from the observed isomer ratio at 86 °C and assumed to be applicable to higher temperatures (see Table 2).

[b] Calculated for 150 °C from AB + BD - AC.

[c] From the observed equilibrium constant.

[d] In PEG 200, a value of 3.6 ± 0.2 kcal mol^{-1} was obtained (data from Tables 2 and 4).



5 **6** **7**

(a) R_1 = Ph, R_2 = Bu^n (b) R_1 = *p*-ClPh, R_2 = Bu^n
(c) R_1 = R_2 = $(CH_2)_3Ph$ (d) R_1 = $(CH_2)_3Ph$, R_2 = Pr^n

DISCUSSION

The regioselectivity of kinetically-controlled triazolisation of 1,1-diphenyl epoxide (**3**) in DMF increases as substrate concentration decreases from 5M and 0.1M (Table 1) and further from 0.1M to 0.01M (Table 2). Most of the kinetic results were obtained using NMP as solvent because it has a higher boiling point than DMF. The results in Table 2 show that the isomer ratio for the kinetically-controlled reaction is independent of temperature in both DMF and PEG 200 and we assume that the same will be true for NMP.

Triazole isomers (**1** and **4** and **6** and **7**) were decomposed at 130-180°C in the presence of excess sodium hydroxide, and the disappearance of starting materials gave good first order kinetics. Presumably the excess base converts the triazole alcohols to the corresponding alkoxides and their decomposition is unimolecular. Under the reaction conditions, 4-isomers rearrange to 1-isomers and diphenylacetaldehyde, a decomposition product of diphenyl epoxide (**3**).[7] The dialkyl derivatives (**6**,**7**, c and d) decompose less readily than the aryl substituted compounds (**6**, **7**, a and b). We assume that decomposition of the 1-isomer (**1**) gives the free energy difference (BD) and of the 4-isomer (**4**) gives AC - see Figure 2. The free energy differences between the triazole isomers **1** and **4** and **6** and **7** were calculated using the Eyring equation from the kinetic data (AB + BD – AC, Figure 2) and also from the observed equilibrium constants. Agreement

between these two values (CD, Table 5) supports the mechanism shown in Figure 1 and shows that the rearrangement is thermodynamically-controlled.

The rate constant for decomposition of the 1-isomer (**1**) varies over 10^3 fold as the substrate concentration varies from 5M to 0.1M (Table 3). As expected there is a strong tendency for the triazole anion and the epoxide to reform the 1-isomer (**1**). The desired competing reaction to achieve decomposition of **1** is removal of epoxide (**3**) by its rearrangement to diphenylacetaldehyde[7] and this becomes relatively more favourable at low substrate concentrations (Table 3).

During attempts to repeat the kinetic studies at substrate concentrations of 0.01M, decomposition products of NMP interfered with the chromatographic analyses and the necessarily large injections of NMP impaired the performance of the HPLC column. We then reverted to DMF as solvent, but reaction rates then depended on the state of the sodium hydroxide, e.g., whether it was crushed or stirred. Also reaction rates depended strongly on whether water was absorbed by the sodium hydroxide. Behaviour in NMP was similar. The most reproducible results were obtained using PEG 200 as solvent. These results show consistent activation parameters for decompositions of **1** and **4** (Table 4); and the rate constant for decomposition of the 4-isomer (**4**) is not significantly affected by the change in concentration from 0.1 to 0.01M. However, the rate of decomposition of the 1-isomer is slightly concentration dependent even at these low concentrations. Hence, the reverse reaction to reform the 4-isomer is prevented effectively because the 1-isomer forms instead, but the epoxide formed by decomposition of the 1-isomer is not trapped with 100% efficiency.

In PEG 200, the free energy difference (CD_{calc}) for **1** and **4** of 3.6 ± 0.2 kcal mol^{-1} for 0.1M solutions and 3.3 ± 0.2 kcal mol^{-1} for 0.01M solutions agree satisfactorily with each other but are slightly lower than values obtained in NMP (4.37[5] and 4.56 ± 0.44 in Table 5). The concentration dependence of the rate constants (Table 3) for decomposition of the 4-isomer (**4**) may be a medium effect because reaction in PEG 200 is slower (Table 4). Alternatively, decomposition of the 4-isomer (**4**) may be reversible. As the rate of decomposition of the 1-isomer (**1**) depends on concentration even below 0.1M (Table 5), a solvent effect is unlikely and a preferred explanation is that this reaction is reversible. Interestingly, the regioselectivity of the kinetically-controlled triazolisation reaction is concentration dependent even below 0.1M concentrations (see Table 2)

General Mechanistic Implications. Nucleophilic displacement of heterocyclic anions (e.g., the triazole anion (**2**)) is a well established mechanism.[8,9] Isomerisations may be catalysed by addition of alkylating agents (alkyl halides[10] or epoxides[11]), leading to nucleophilic displacement of neutral alkyl triazole from a quaternary salt.[10] Our proposal that quaternary salt formation could also occur at 350 °C in the absence of added alkylating agents[2] is supported by recent work on the rearrangement of 4-alkyl-3,5-diphenyltriazoles.[3] As well as rearrangement to the 1-alkyl derivative (37%) there was a 43% yield of dealkylated product.[3] Hence the 3,5-diphenyltriazole anion is implicated in this reaction. There are also reports of "co-catalysts" such as air, water and aza-isobutyronitrile AIBN.[4] Our work is consistent with water as a possible solid-liquid phase transfer catalyst but it is not clear why AIBN should be regarded as a "co-catalyst", and experimental support is lacking.[4]

CONCLUSIONS

The free energy data (Table 5) are consistent with a thermodynamically controlled process for rearrangement of 4- to 1-alkyl triazoles, which can be achieved in good yield when decomposition of the epoxide is minimised.[4] Nucleophilic displacement of the triazole anion explains these and other[2] observations. Crossover experiments support an intermolecular mechanism.

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EXPERIMENTAL

General. NMR spectra were obtained on Varian XL-100 or Perkin Elmer-Hitachi R24B (60 MHz) spectrometers, mass spectra were obtained using a VG12-253 quadrupole instrument and IR spectra were recorded on a Philips SP1050 instrument. The HPLC equipment as described previously[12] included a Hewlett Packard electronic integrator (HP3390A). Results were obtained with 5 μm Spherisorb ODS2 eluted with methanol/water (60%) at 25°C; flow rate = 1 mL/min; λ = 255 nm; absorbance range = 0.1. Standard solutions of the individual triazole isomers were prepared and their relative response factors obtained. For more recent work including all analyses of 0.01M solutions, the equipment was a "Promis" autosampler, a LDC Milton Roy "Constametric 3000" solvent pump, a LDC "Spectromonitor 3100" variable wavelength UV detector (Absorbance range 0.02), and a LDC "Cl-4100" computing integrator.

1,1-Diphenyl-2-(1,2,4-triazol-1-yl)ethanol (1) and 1,1-Diphenyl-2-(1,2,4-Triazol-4-yl)ethanol (4) A mixture of 1,1-diphenylepoxide[13] (3) (5.00g, 0.026 mol), 1,2,4-triazole (1.79g, 0.026 mol), and potassium carbonate (3.59g, 0.026 mol) in DMF (13 mL) was stirred at 86 °C for 1 hour. After evaporating the solvent, the solid residue was treated with water (100 mL) and extracted with CH_2Cl_2 (100 mL). The organic layer was dried (Na_2SO_4) and then evaporated to give a white solid (6.38g, 94%), an 87/13 mixture of **1** and **4**. This solid (5g) was extracted with boiling toluene (2 x 200 mL) and was filtered hot; on cooling a solid was collected which was recrystallised from toluene and then methanol to give white crystals of 1,1-diphenyl-(1,2,4-triazol-1-yl)ethanol (**1**) (3.35g, 67%): mp 132 °C; IR ν_{max} (KBr) 3300, 1455 cm^{-1}; m/z 183 (59%), 146 (38%), 105 (100%); ^1H NMR ($CDCl_3$) δ 4.46 (broad singlet, 1H, exch, OH), δ 4.97 (s, 2H, CH_2), δ 7.24-7.62 (m, 10H, ArH), δ 7.75 (s, 1H), δ 7.88 (s, 1H). Anal Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.3, H, 5.8, N, 15.9.

The material insoluble in toluene was dissolved in CH_2Cl_2 (50 mL) and extracted with 0.1M HCl (50 mL). Neutralisation of the aqueous layer with 1M NaOH gave white crystals, which were isolated by extraction into CH_2Cl_2. Evaporation of the organic layer and recrystallisation of the residue from methanol gave white crystals of 1,1-diphenyl-(1,2,4-triazol-4-yl)ethanol (**4**) (0.34g, 7%): mp 253 °C; ν_{max} (KBr) 3160, 1455 cm^{-1}; m/z 183 (79%), 105 (100%); ^1H NMR (95% $CDCl_3$, 5% D_6-DMSO) δ 4.88 (s, 2H, CH_2), δ 7.20-7.56 (m, 10H, ArH), δ 7.95 (s, 2H). Anal Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.4; H, 5.6; N, 15.6.

1-n-Butyl-1-phenyl epoxide (5a).[14] To a stirred mixture of valerophenone (4.94g, 0.030 mol) and trimethylsulphonium iodide (9.32g, 0.046 mol) in t-butanol (28 mL) at 50 °C was added potassium hydroxide (5.01g, 0.076 mol). After 6 hours the t-butanol was removed by distillation and the residue treated with water (75 mL), 1.3M sodium hypochlorite (13 mL) and toluene (50 mL). The organic layer was collected and washed with water (6 x 75 mL) until neutral. Drying (Na_2SO_4), followed by evaporation left a pale yellow liquid that was distilled under reduced pressure to give 1-n-butyl-1-phenyl epoxide (**5a**) as a colourless liquid (4.90g, 91%). Further purification proceeded using flash column chromatography (silica gel 40-63 μm, toluene): b 0.01 44 °C; ν_{max} (NaCl) 2960, 1460 cm^{-1}; m/z 176 (11%), 175 (26%), 147 (32%), 117 (15%), 115 (15%), 91 (100%); ^1H NMR ($CDCl_3$) δ 0.82 (t, 3H, CH_3), δ 1.30 (m, 4H, CH_2CH_2), δ 1.92 (t, 2H, CH_2), δ 2.74 (q, 2H, CH_2), δ 7.25 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 13.9 (q, CH_3), δ 22.8 (t, CH_2), δ 27.1 (t, CH_2), δ 35.3 (t, CH_2), δ 55.4 (t, CH_2), δ 60.4 (s, C), δ 127.2 (m, Ar).

1-n-Butyl-1-phenyl-2(1,2,4-triazol-1-yl)ethanol (6a) and 1-n-Butyl-1-phenyl-2-(1,2,4-triazol-4-yl)ethanol (7a). A mixture of 1-n-butyl-1-phenyl epoxide (**5a**) (7.65g, 0.043 mol), 1,2,4-triazole (3.00g, 0.043 mol) and potassium carbonate (6.00g, 0.43 mol) in DMF (22 mL) was stirred at 86 °C for 4 hours. Evaporation of the solvent gave a solid residue that was treated with water (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic layer was dried (Na_2SO_4) and then evaporated to give a viscous oil which slowly solidified. This solid was extracted with boiling toluene (2 x 200 mL) and the procedure described for **1** gave white crystals of 1-n-butyl-1-phenyl-2-(1,2,4-triazol-1-yl)ethanol (**6a**) (7.88g, 74%): mp 81°C; m/z 188 (27%), 164 (11%), 163 (74%), 146 (26%), 83 (100%), ^1H NMR ($CDCl_3$) δ 0.78 (t, 3H, CH_3), δ 1.20 (m, 4H, CH_2CH_2), δ 1.88 (t, 2H, CH_2), δ 4.36 (s, 2H, CH_2), δ 4.57 (broad singlet, 1H, exch, OH), δ 7.27 (m, 5H, ArH), δ 7.71 (s, 1H), δ 7.78 (s, 1H). Anal Calcd for $C_{14}H_{19}N_3O$: C, 68.48; H, 7.81; N, 17.12. Found: C, 68.4; H, 8.0; N, 17.3.

The material insoluble in toluene, when treated as described for **4**, gave white crystals of 1-n-butyl-1-phenyl-2-(1,2,4-triazol-4-yl)ethanol (**7a**) (0.78g, 7%): mp 149 °C; m/z 246 (3%), 163 (12%), 105 (11%), 91 (18%), 83 (100%), ^1H NMR ($CDCl_3$) δ 0.80 (t, 3H, CH_3), δ 1.21 (m, 4H, CH_2CH_2), δ 4.38 (s, 2H, CH_2), δ 4.60 (broad singlet, 1H, exch, OH), δ 7.23 (m, 5H, ArH), δ 7.76 (s, 2H).

1-(*p*-chlorophenyl)-1-n-butyl epoxide (5b). To a stirred mixture of *p*-chlorovalerophenone (9.84g, 0.050 mol) and trimethylsulphonium iodide (15.22g, 0.074 mol) in *t*-butanol (45 ml) at 40 °C was added KOH (8.35g, 0.126 mol). After 4 hours the *t*-butanol was removed by distillation and the residue was treated as for **5a**. A spinning band distillation gave 1-(*p*-chlorophenyl)-1-n-butyl epoxide (**5b**) as a colourless liquid (8.64g, 82%): b 0.2 94 °C; m/z 209 (26%), 211 (9%), 181 (46%), 125 (100%); ^1H NMR ($CDCl_3$) δ 0.84 (t, 3H, CH_3), δ 1.30 (m, 4H, CH_2CH_2), δ 1.89 (t, 2H, CH_2), δ 2.74 (q, 2H, CH_2), δ 7.24 (s, 4H, ArH); Anal Calcd for $C_{12}H_{15}ClO$: C, 68.4; H, 7.2; Cl, 16.8. Found: C, 67.9; H, 7.6; Cl, 16.9.

1-(*p*-chlorophenyl)-1-n-butyl-2-(1,2,4-triazol-1-yl)ethanol (6b) and 1-(*p*-chlorophenyl)-1-n-butyl-2-(1,2,4-triazol-4-yl)ethanol (7b). A mixture of 1-(*p*-chlorophenyl)-1-n-butyl epoxide (5.00g, 0.024 mol), 1,2,4-triazole (1.64g, 0.024 mol) and potassium carbonate (3.59g, 0.026 mol) in DMF (7 mL) was stirred at 86 °C for 2 hours. Evaporation of the solvent gave a solid residue that was purified as described for **6a** to give white crystals of 1-(*p*-chlorophenyl)-1-n-butyl-2-(1,2,4-triazol-1-yl)ethanol **5b** (4.71g, 71%): mp 93 °C; ^1H NMR ($CDCl_3$) δ 0.85 (t, 3H,

CH_3), δ 1.25 (m, 4H, CH_2CH_2), δ 1.80 (m, 2H, CH_2), δ 4.38 (s, 2H, CH_2), δ 4.64 (broad singlet, 1H, exch, OH), δ 7.22 (s, 4H, ArH), δ 7.68 (s, 1H) δ 7.80 (s, 1H). Anal Calcd for $C_{14}H_{18}N_3OCl$: C, 60.1; H, 6.5; N, 15.0. Found: C, 60.0; H, 6.7; N, 14.7.

Material insoluble in toluene, when treated as described for **4** gave white crystals of 1-(*p*-chlorophenyl)-1-n-butyl-2-(1,2,4-triazol-4-yl)ethanol (0.62g, 9%): mp 170 °C; m/z 280 (0.3%), 197 (9%), 139 (5%), 125 (5%), 111 (7%), 83 (100%); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, CH_3), δ 1.26 (m, 4H), δ 1.78 (t, 2H), δ 4.10 (broad singlet, 1H, exch), δ 4.35 (s, 2H), δ 7.22 (s, 4H, ArH), δ 7.74 (s, 2H).

1,1-di(3-phenylpropyl) epoxide (5c). Ethyl formate and 3-phenylpropyl magnesium bromide gave 1,7-diphenylheptan-4-ol, which was oxidised and epoxidised to 1,1-di(3-phenylpropyl) epoxide (**5c**). Purification by column chromatography (SiO_2, toluene) gave a colourless viscous liquid (0.90g, 87%): b 0.005 149 °C; ν_{max} (NaCl) 2980, 1500, 1460 cm^{-1}; m/z 249 (6%), 157 (6%), 143 (20%), 129 (11%), 104 (100%), 91 (55%); ^{1}H NMR ($CDCl_3$) δ 1.58 (m, 8H, 4 x CH_2), δ 2.47 (m, 6H, 3 x CH_2), δ 7.13 (m, 10H, 2 x ArH); ^{13}C NMR ($CDCl_3$) δ 26.5 (t, CH_2), δ 33.8 (t, CH_2), δ 35.8 (t, CH_2), δ 52.2 (t, CH_2), δ 59.0 (s, C), δ 127 (m, Ar). Anal Calcd for $C_{20}H_{24}O$: C, 85.67; H, 8.63. Found: C, 85.9; H, 8.7.

1,1-di(3-phenylpropyl)-2-(1,2,4-triazol-1-yl)ethanol (6c) and 1,1-di(3-phenylpropyl)-2-(1,2,4-triazol-4-yl)ethanol (7c). A mixture of 1,1-di(3-phenylpropyl) epoxide (**5c**) (2.00g, 7.14 x 10^{-3} moles), 1,2,4-triazole (0.50g, 7.25 x 10^{-3} moles) and potassium carbonate (1.00g, 7.25 x 10^{-3} moles) in DMF (3.5 mL) was stirred at 86 °C for 48 hours. Evaporation of the solvent gave a solid residue that was treated with water (50 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The organic layer was collected, dried (Na_2SO_4) and then evaporated to give a yellow oil of the crude **6c/7c** mixture (2.30g, 6.577 x 10^{-3} moles, 92% yield, 86% **6c** to 14% **7c**).

A solution of this oil (0.35g, 1 x 10^{-3} moles) in methanol (1 mL) was injected in 20 μL quantities into a small scale preparative reverse phase HPLC apparatus (5 μm Spherisorb ODS2, 80% aqueous methanol). For each of 25 injections the fraction relating to **6c** was collected and combined. The combined fractions were evaporated to give pure **6c** (0.1062g, 3.04 x 10^{-4} moles): b 0.005 170 °C; ν_{max} (KBr) 3365, 2962, 1518, 1460 cm^{-1}; m/z 349 (4%), 331 (12%), 230 (9%), 131 (15%), 117 (14%), 106 (27%), 104 (100%); ^{1}H NMR ($CDCl_3$) δ 1.16-1.80 (m, 8H, -$(CH_2)_2$-), δ 2.52 (t, 4H, Ar-CH_2), δ 3.41 (broad singlet, 1H, exch, OH), δ 4.00 (s, 2H, N-CH_2), δ 7.16 (m, 10H, ArH), δ 7.76 (s, 1H), δ 7.93 (s, 1H); Anal Calcd for $C_{22}H_{27}N_3$: C, 75.6; H, 7.8; N, 12.0. Found: C, 75.3; H, 7.6; N, 11.8.

1-Phenylheptan-4-ol. A solution of n-butyraldehyde (17.75g, 0.246 moles) in anhydrous tetrahydrofuran (THF) (6 mL) was added dropwise to a stirred solution of 3-phenylpropylmagnesium bromide prepared from magnesium (6.00g, 0.247 moles) and 1-bromo-3-phenylpropane (48.88g, 0.245 moles)] in anhydrous THF (54 mL) keeping the temperature below 65 °C. After being stirred for 3 hours at 45 °C, water (150 mL) was added and the THF was removed by distillation. On cooling, saturated ammonium chloride solution (150 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 x 150 mL). The organic layer was then washed with saturated ammonium chloride solution (2 x 400 mL) followed by water (3 x 400 mL) before drying (Na_2SO_4). Evaporation of the solvent afforded a yellow oil that on reduced pressure distillation gave 1-phenylheptan-4-ol (42.49g, 0.221 moles,

90% yield): b 0.1 104 °C; ν_{max} (NaCl) 3275, 2970 cm^{-1}; m/z 174, 131, 117, 104 (100%), 91, 77; ^1H NMR ($CDCl_3$) 0.95 (t, 3H, CH_3), δ 1.1-1.9 (m, 8H, $-CH_2-CH_2-$), δ 2.05 (s, 1H, exch, OH), δ 2.58 (t, 2H, Ar-CH_2-), δ 3.25 (m, 1H, CH), δ 7.05 (m, 5H, ArH); Anal Calcd for $C_{13}H_{20}O$: C, 81.2; H, 10.5. Found: C, 81.4; H, 10.4.

1-Phenylheptan-4-one. A solution (230 mL) [prepared from sodium dichromate (120g, 0.4 moles), concentrated sulphuric acid (54 mL, 0.97 moles) and water (600 mL) was added to a rapidly stirred solution of 1-phenylheptan-4-ol (40.21g, 0.209 moles) in acetone (400 ml) at room temperature. After being stirred for 3 hours at room temperature, the acetone was removed and the mixture extracted with CH_2Cl_2 (2 x 250 mL). The combined extracts were washed until neutral, dried and evaporated. A reduced pressure distillation gave 1-phenylheptan-4-one (36.67g, 0.193 moles, 92.3% yield): b 0.1 94 °C; ν_{max} (NaCl) 1695 cm^{-1}; m/z 190, 147, 131, 117, 104 (100%), 91, 77; ^1H NMR ($CDCl_3$) δ 0.85 (t, 3H, CH_3), δ 1.4 to δ 2.0 (m, 4H, CH_2), δ 2.1 to 2.8 (m, 6H, $ArCH_2$ and CH_2CO), δ 7.07 (m, 5H, ArH).

1-(3-phenylpropyl)-1-propyl epoxide (5d). A solution of trimethylsulphonium iodide (46.9g, 0.226 moles) in dimethyl sulfoxide (DMSO) (150 mL) was added over 5 minutes to a stirred mixture of sodium hydride (6.90g, 0.288 moles) in DMSO (350 mL) at 30 °C under nitrogen. After being stirred for a further 10 minutes at 30 °C, a solution of 1-phenylheptan-4-one (35.18g, 0.185 moles) in DMSO (50 mL) was added and the mixture stirred for a further 8 hours at 50 °C. The mixture was then treated with water (500 mL) and extracted with petroleum ether (60-80 °C, 2 x 250 mL). The extract was dried (Na_2SO_4) and evaporated to give 1-(3-phenylpropyl)-1-propyl epoxide **5d** (29.77g, 0.146 moles, 78.9% yield): ν_{max} (NaCl) 3000, 1520 cm^{-1}; m/z 174, 129, 117, 104 (100%), 91; ^1H NMR ($CDCl_3$) δ 0.98 (t, 3H, CH_3) δ 1.1 to δ 1.9 (m, 8H, $-CH_2CH_2-$), δ 2.6 (s, 2H), δ 2.7 (t, 2H, $ArCH_2$), δ 7.15 (m, 5H, ArH).

1-(3-phenylpropyl)-1-propyl-2-(1,2,4-triazol-1-yl)ethanol (6d) and 1-(3-phenylpropyl)-1-propyl-2-(1,2,4-triazol-4-yl)ethanol (7d). A mixture of 1-(3-phenylpropyl)-1-propyl epoxide (25.02g, 0.123 moles), 1,2,4-triazole (8.49g, 0.123 moles) and potassium carbonate (18.40g, 0.133 moles) in DMF (40 mL) was stirred at 86 °C for 2 hours. Evaporation of the solvent gave a solid residue that was treated with water (200 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic layer was collected, dried (Na_2SO_4) and then evaporated to give a yellow oil of the crude **6d/7d** mixture (31.65g, 0.116 moles, 94.3% yield). The oil (5.00g, 0.0183 moles) was dissolved in boiling toluene (200 mL) and shaken with 0.1M HCl (2 x 50 mL). The organic layer was collected and evaporated to give a yellow liquid of 1-(3-phenylpropyl)-1-propyl-2-(1,2,4-triazol-1-yl)ethanol **6d** (3.56g, 0.013 moles) which was purified by column chromatography (silica and methanol/$CHCl_3$): ν_{max} (NaCl) 3300, 2895, 1460 cm^{-1}; m/z 273 (0.2%), 255 (1.4%), 174 (3.0%), 154 (3.0%), 131 (24%), 117 (15%), 106 (18%), 104 (100%), 91 (46%); ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, CH_3), δ 1.41 to δ 1.8 (m, 8H, CH_2CH_2), δ 2.65 (t, 2H, $ArCH_2$), δ 4.05 (broad singlet, 1H, exch, OH), δ 4.12 (s, 2H, N-CH_2), δ 7.15 (s, 5H, ArH), δ 7.90 (s, 1H), δ 8.05 (s, 1H). HR-FABMS: Found: 274.192; Calculated for $C_{16}H_{24}N_3O$, 274.1919.

The aqueous layer was shaken with hot toluene (2 x 50 mL) before neutralising with 1M NaOH and extraction into CH_2Cl_2 (100 mL). Evaporation of the organic layer after drying ($MgSO_4$) gave a solid of 1-(3-phenylpropyl)-1-propyl-2-(1,2,4-triazol-4-yl)ethanol) **7d** (0.32g, 1.17 x 10^{-3} moles), which was recrystallised from CH_2Cl_2/petrol: mp 125-127 °C;: ν_{max} (KBr) 3310, 2895 cm^{-1}; m/z 273 (1.0%), 255

(3%), 230 (3%), 191 (4%), 154 (13%), 131 (8%), 117 (13%), 106 (15%), 104 (67%), 91 (42%), 83 (100%); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, CH_3), δ 1.2 to δ 1.8 (m, 8H, CH_2CH_2), δ 2.60 (t, 2H, $ArCH_2$), δ 3.80 (broad singlet, 1H, exch, OH), δ 3.95 (s, 2H, N-CH_2), δ 7.20 (m, 5H, ArH), δ 8.10 (s, 2H, 3). HR-FABMS: Found: 274.192; Calculated for $C_{16}H_{24}N_3O$, 274.1919.

Cross Product Experiments.

1. A mixture of 1,1-diphenyl-2-(1,2,4-triazol-4-yl)ethanol **4** (0.053g, 2 x 10^{-4} moles), 1-n-butyl-1-phenyl epoxide **5a** (0.070g, 4 x 10^{-3} moles) and sodium hydroxide (0.160g, 4 x 10^{-3} moles) in NMP (2 mL) was stirred at 138 °C for one hour. The mixture was then quenched using liquid nitrogen, filtered and analysed by HPLC. The chromatogram showed the presence of 1-n-butyl-1-phenyl-2-(1,2,4-triazol-1-yl)ethanol (**6a**) as well as the expected product of the isomerisation (**1**) and diphenylacetaldehyde.
2. To a mixture of 1-n-butyl-1-phenyl-2-(1,2,4-triazol-4-yl)ethanol (**7a**) (0.0491 g, 2 x 10^{-4} moles) and sodium hydroxide (0.160g, 4 x 10^{-3} moles) in NMP (2 mL) at 138 °C was added with stirring 1,1-diphenylethylene oxide **3** (0.392g, 0.002 moles) in five portions over one hour. After a further 15 minutes a sample of the mixture was withdrawn and quenched. After filtration the sample was analysed by HPLC. The chromatogram showed the presence of 1,1-diphenyl-2-(1,2,4-triazol-1-yl)ethanol) (**1**).
3. A mixture of 1-n-butyl-1-phenyl-2-(1,2,4-triazol-4-yl)ethanol **8a** (0.0491g, 2 x 10^{-4} moles); 1,1-diphenylethylene bromohydrin (0.111g, 4.3 x 10^{-3} moles) and sodium hydroxide (0.160g, 4 x 10^{-3} moles) in NMP (2 mL) was stirred at 138 °C for one hour. The mixture was then quenched and filtered and again showed the presence of 1,1-diphenyl-2-(1,2,4-triazol-1-yl)ethanol (**1**).

Kinetic Studies. **Decomposition of 1,1-diphenyl-2-(1,2,4-triazol-4-yl)ethanol (4) by Excess Sodium Hydroxide**. To a solution of **4** (0.130g, 4.91 x 10^{-4} mol) in NMP (0.1 mL) at a fixed temperature between 138 °C and 180 °C was added sodium hydroxide (0.02g, 5 x 10^{-4} mol) and the mixture stirred. Samples were withdrawn at intervals (dependent on the temperature), quenched and dissolved in methanol, and the disappearance of **4** was monitored by HPLC. Rate constants were obtained as described previously,[12] and other kinetic studies were carried out similarly.

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