

Reaction of Sodium Azide with 1,1'-Dicyclohexenyl-Diepoxides

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ABSTRACT: Nucleophilic ring opening of *dl* and *meso* 1,1'-dicyclohexenyl diepoxides by sodium azide in dioxane and aqueous alcoholic medium give the corresponding azidoalcohols. The obtention of departure diepoxides from diazidoalcohols by the reaction with sodium hydride shows the anti position of OH and N₃ groups.

KEY WORDS: Sodium azide, 1,1' – Dicyclohexenyl – diepoxides, Nucleophilic opening, Azidoalcohols, Trans diaxial

INTRODUCTION

Diepoxides present interesting biological properties [1]. The compounds are also considered as important starting materials in resin industry [2]. Besides, azide derivatives are used extensively in organic synthesis specially for primary amines preparation [3].

In continuation of our earlier work on diastereomeric ring opening of diepoxides **1** and **2** [4], we now report on the ring opening of these epoxides by sodium azide.

When *dl* diepoxide **1** was refluxed with sodium azide in aqueous 80% ethanol in the presence of ammonium chloride, azido alcohol **3** was obtained in 83% yield (Scheme 1). The structure of **3** was elucidated through spectroscopic data. The IR spectrum showed OH and N₃ absorptions at 3475 cm⁻¹ and 2111 cm⁻¹ respectively.

¹H NMR showed for CH(N₃) protons as a multiplet at 3.87 ppm. The OH protons which were observed at 3.75 ppm as a singlet disappeared after addition of trifluoroacetic acid.

In accordance with the symmetry of the molecule ¹³C NMR of **3** exhibits six resonances. The mass spectrum of **3** showed a low intensity of molecular ion peak at *m/e*: [M⁺] 280.

When diepoxide **1** was refluxed with sodium azide in dioxane solvent [5], the reaction proceeds slowly and besides the compound **3**, the product **4** is also obtained.

The IR Spectrum of **4** showed the OH, C-H epoxide and azide absorptions at 3533 cm⁻¹, 3010 cm⁻¹, and 2094 cm⁻¹ respectively.

¹H NMR showed one epoxide proton, one CH(N₃) proton and OH proton at 3.65 ppm, 3.8 ppm and 2.87 ppm respectively.

¹³C NMR of **4** showed 12 absorptions justifying the non-symmetrical structure for compound **4**. The mass spectrum of **4** showed a molecular ion peak [M⁺] = 237.

The reaction rate is faster in ethanol compared to dioxane which is attributed to the hydrogen bond formation [6] between the protic solvent and oxygen ring

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epoxide which facilitates the epoxide ring opening by N_3^- .

When **3** is reacted with sodium hydride and iodomethane to methylate the OH group, the methylated compound is not obtained and we observed the regeneration of dl diepoxide **1**. (the same melting point, R_f and spectroscopic data).

Repeating the same reaction without iodomethane, the same result is obtained. The intramolecular attack of OH anion on the azide carbon, regenerates the epoxide ring. Tobe and coworkers[7] have reported the methylation of OH group of Cis-2-Phenyl-2-azido-1-cyclohexanol. This proves the anti position of OH and N_3 in **3**.

In the reaction of meso diepoxide **2** with sodium azide[5] and ammonium chloride (in aqueous 80% ethanol), after 145 hours of reflux, the transformation rate of **2** is maximum and the products **5** and **6** are obtained (scheme 1). The spectroscopic data for **5** are in agreement with the azido alcohol. The IR spectrum shows the OH and azide absorptions at 3502 cm^{-1} and 2102 cm^{-1} respectively.

^1H NMR shows the $\text{CH}(\text{N}_3)$ protons as a doublet at 3.92 ppm. OH protons are seen as singlet at 3.25 ppm (disappeared by addition of $\text{CF}_3\text{CO}_2\text{H}$). ^{13}C NMR, spectra

show six absorption peaks reflecting the fact that the product has a symmetrical structure.

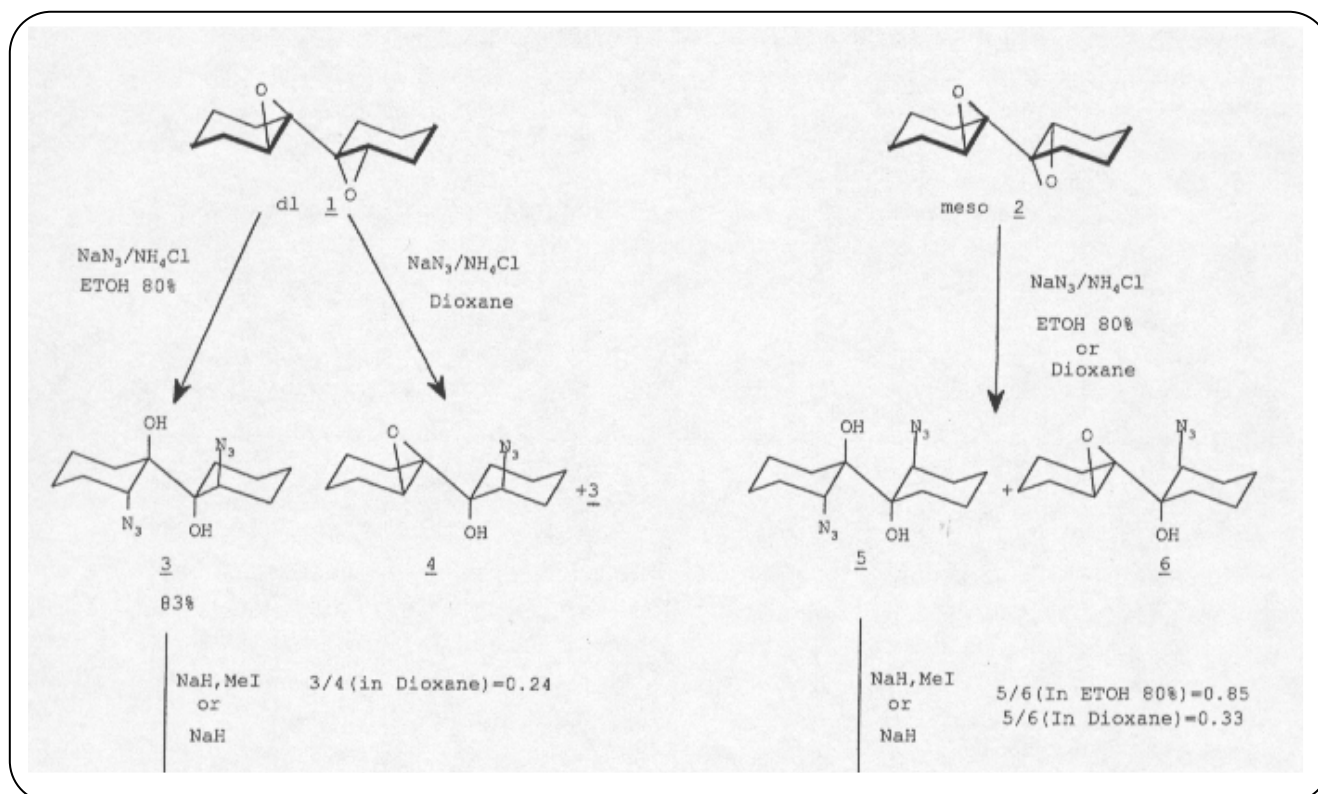
The spectroscopic data for **6** proves that one epoxide ring is still present. IR spectrum shows a net absorption at 3446 cm^{-1} for OH (alcohol) and there are absorptions at 3012 cm^{-1} and 2106 cm^{-1} which are attributed to the C-H epoxide and azide respectively.

^1H NMR shows a triplet at 3.77–3.78 ppm for the $\text{CH}(\text{N}_3)$ proton. The doublet observed at 3.25 ppm is attributed to epoxide ring proton.

The alcoholic and cyclohexane ring protons are seen at 1.31–1.99 ppm.

The compound **6** has a non symmetrical structure because of twelve absorptions observed in ^{13}C NMR.

If the meso diepoxide **2** is refluxed with sodium azide and ammonium chloride in dioxane as solvent, compounds **5** and **6** are obtained and after 195 hours of reflux, the unreacted **2** is minor. Preferential formation of **6** confirms the role of ethanol in epoxide ring opening via the hydrogen bond formation[6]. The compound **5** when reacted with sodium hydride and iodomethane (or sodium hydride only), the meso diepoxide **2** is obtained which demonstrate the anti position of OH and N_3 in **5**.



Scheme 1

The results obtained explain the anti position of OH and N₃ in compounds **3** and **5**.

According to the literature, the ring opening of diepoxides **1** and **2** takes place on trans diaxial [8]. This stereochemistry is a result of stereoselectivity SN₂ type displacement.

EXPERIMENTAL SECTION

IR spectra were performed on an FT-IR shimadzu – 400. The ¹H NMR and ¹³C NMR were recorded in CDCl₃ on a Bruker 80 MHZ using TMS as the internal standard. Mass spectra were scanned on Finigan-TSQ-70.

TLC and column chromatography were performed on silicagel (Merck). Diepoxides (meso and dl) were prepared from 1,1'- Dicyclohexenyl according to published procedure [9]. Para-nitro perbenzoic acid is prepared according to literature [10].

Reaction of diepoxide (dl) **1** with sodium azide in aqueous 80% ethanol.

Diepoxide (dl) **1** (1.0 gr, 5.2 mmol) was dissolved in aqueous 80% ethanol (35 ml). To this solution and under stirring sodium azide (0.93 g, 14.3 mmol) and ammonium chloride (0.76 g, 14.5 mmol) were added. The reaction mixture was refluxed. The colorless solution became yellowish brown. After 120 hours reflux the major part of diepoxide disappeared (monitored by TLC). The solvent was evaporated and water was added. The organic materials were extracted by diethyl ether (50 ml × 4). The combined organic layers was dried over anhydrous sodium sulfate and the solvent were evaporated to dryness. The crude product was subjected to column chromatography over silica gel using diethyl ether / petroleum ether (40-60°C) : 50/50 to give (1.2 gr, 83%) product **3** as white crystal.

- mp: 155-157°C R_f: 0.3 (the same eluent).
- IR (KBr) : 3477.4, 2954.7, 2933.5, 2111.9, 1442.6, 1384.8, 1357.8, 1272.9, 1242, 1159, 1124.4, 1006.7, 979.7, 916.1, 871.7, 675, 551.6 cm⁻¹.
- ¹H NMR δ (ppm): 1.56 – 2.10 (m, 16H), 3.73 (s, 2H, OH, disappeared by addition of CF₃CO₂H), 3.88 (broad, 2H, CH(N₃)).
- ¹³C NMR δ (ppm) : 19.70, 20.55, 25.14, 26.35, 70, 74.
- Nitrogen percent (Elemental analysis) : 30.5 (Experimental), 30 (calculated) correspond to C₁₂H₂₀O₂N₆.

- MS : m/e (relative intensity) : 41(100), 43(39), 55(63), 67(43), 70(26), 81(36), 84(33), 97(31), 98(47), 109(11), 124(5), 152(4), 163(4), 181(2), 209(1), 248(1), 280(1), 281(1).

Reaction of diepoxide (dl) **1** with sodium azide in dioxane.

In a two necked round – bottomed flask fitted with a condenser, diepoxide (dl) **1** (1gr, 5.2mmol) was solubilized in dioxane (9 ml). Sodium azide (0.93 g, 14.3mmol), ammonium chloride (0.76 gr, 14.5 mmol) and water (2.4 ml) were added to the above solution with stirring. After 160 hours reflux, the major part of diepoxide **1** was consumed (monitored by TLC). The solvent was evaporated. To the solid residue obtained water was added and organic materials were extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulfate and the crude obtained after evaporation of solvent was subjected to column chromatography using diethyl ether/-petroleum ether (40-60°C): 50 / 50.

The compounds obtained are as follow:

- Starting diepoxide (dl) **1** (140 mg).
- A mixture of starting diepoxide **1** and **3** (70 mg).
- Compound **3** (200 mg, 14%), The melting point and spectral analysis of **3** is identical with the epoxide ring opening product using sodium azide in aqueous ethanol solvent.
- Monoepoxide **4** (680 mg, 55%), mp = 73-74°C with the following spectroscopic data.

IR (KBr): 3537.2, 3010.7, 2981.7, 2975.5, 2094.5, 1436.8, 1382.8, 1355.8, 1296, 1249, 1159.1, 1130.2, 1074, 1041, 993.2, 939.2, 900.7, 825.4 cm⁻¹.

¹H NMR δ (ppm) : 1.61 – 2.05 (m, 16H), 2.27 (s, H, OH, disappeared by addition of CF₃- CO₂H), 3.66 (broad, 1H), 3.85 (broad, 1H).

¹³C NMR δ (ppm) : 19.34, 20.04, 22.92, 23.31, 23.88, 24.45, 28.39, 31.23, 59.45, 66.38, 67.99, 73.30.

MS: m/e (relative intensity) : 35(22), 41(65), 67(25), 79(5), 83(23), 85(20), 98(100), 112(15), 123(1), 140(1), 150(1), 163(1), 174(1), 210(1), 237(1).

Reaction of **3** with sodium hydride and iodomethane.

In a 100 ml two necked round – bottomed flask, compound **3** (0.2 g, 0.71 mmol) was solubilized in anhydrous tetrahydrofuran (50 ml). Excess of sodium

hydride (60%) was added to this solution with stirring. After stirring (1h) and then refluxing (3h), 8.9 gr (excess) of iodomethane was added gradually. The reaction mixture was refluxed again for 4 hours to disappearance of **3** (TLC). The reaction mixture was allowed to cool to room temperature. Crushed ice was added to the mixture and solvent was evaporated. The residue was extracted by dichloromethane (50 ml×3). The organic layer was dried over anhydrous sodium sulfate. The crude product was subjected to column chromatography using diethyl ether/petroleum ether (40-60°C) : 80/20 to yield a white solid (0.12 g, 87%) which its melting point, ¹H NMR and IR spectral data correspond to diepoxide (dl) **1**.

¹³C NMR δ (ppm) : 19.52 , 20.05 , 24.55 , 25.04 , 55.82, 61.42.

Reaction of meso diepoxide **2 with sodium azide in aqueous 80% ethanol.**

This reaction was carried out in exactly the same way as reaction 1 . To the solution of meso diepoxide **2** (0.400 g, 2.06 mmol) in 80% aqueous ethanol (15 ml), ammonium chloride (0.304 g, 5.7 mmol) and sodium azide (0.373 g, 5.7 mmol) were added. After 145 hours reflux, the crude product was subjected to column chromatography using diethyl ether/petroleum ether (40-60°C) : 70/30. The following products were obtained.

- White solide **5** (0.22 g, 14%) , R_f = 0.73 (same eluent), mp : 118 - 120°C

Nitrogen percent (elemental analysis) : 30.5 (experimental), 30.8 (calculated) correspond to C₁₂H₂₀O₂N₆ .

IR (KBr): 3529.5 , 2974.0 , 2868.2 , 2102.2, 1438.6 , 1384.8, 1357.8, 1321.1, 1263.3 , 1188, 1099.3, 1002.9 , 937.3, 871.7 cm⁻¹.

¹H NMR δ (ppm) : 1.25- 2.24 (m, 16H) , 3.25 (s , 2H) , disappeared after addition of CF₃ CO₂H , 3.87-3.95 (t, 2H, CH(N₃)).

¹³C NMR δ (ppm) : 20.60 , 20.81 , 25.75 , 26.27 , 61.91, 75.09.

A mixture of monoepoxide **6** and meso diepoxide **2** (0.16 g).

- Mono epoxide **6** (0.22 g , 16.3%) as a colorless solid, mp: 112 - 113°C , R_f=0.45 (same eluent).

Nitrogen percent (elemental analysis): 17.7 (experimental), 17.72 (calculated) correspond to C₁₂H₁₈O₂N₃.

IR KBr) : 3012.6 , 2950, 2894 2446.7 , 2106.1, 1465, 1353.9 , 1315.1 , 1290.3 , 1159.1 , 1095.9, 1039.5, 966.2, 883.3 cm⁻¹.

¹H NMR δ (ppm) : 1.31 – 1.99 (m , 18H) , 3.22-3.28 (t, 1H) , 3.78 – 3.81 (t, 1H).

¹³C NMR δ (ppm): 19.31 , 19.65, 19.8, 19.90, 23.3, 24.23, 25.47, 26.39, 57.67, 61.57, 63.82, 73.43.

Reaction of meso diepoxide **2 with sodium azide in dioxane.**

In a procedure similar to reaction 2 , to the solution of meso diepoxide **2** (0.18 g 0.93 mmol) in dioxane (5 ml), ammonium chloride (0.1 g, 1.86 mmol), sodium azide (0.12 g , 1.85 mmol) and water (1 ml) were added. After 195 hours reflux, the crude product was subjected to column chromatography over silica gel using diethyl ether/petroleum ether (40 - 60°C) : 70/30. The following products were obtained.

- Compound **5** (0.06 g, 23%) , mp : 118-120°C

- Mixture of **5** and meso diepoxide **2** (0.03 g).

- Mixture of meso diepoxide **2** and mono epoxide **6** (0.05g).

- Mono epoxide **6** (0.15g , 68%) which melting point and spectroscopic data is the same with the product obtained from the ring opening of meso diepoxide in aqueous 80% ethanol solution.

Reaction of **5 with Sodium hydride and iodomethane.**

This reaction was carried out in exactly the same way as **3** with iodo methane and sodium hydride in excess, using **5** (0.1 g, 0.357 mmol). The crude product was subjected to column chromatography over silica gel 60 using diethyl ether / petroleum ether (40-60°C) : 70/30 as eluant to yield a white solide (50mg, 72%) which its melting point, ¹H NMR and IR spectral data correspond to diepoxide **2**.

¹³C NMR δ (ppm) : 19.52 , 20.05 , 24.55, 25.04, 55.62, 61.42.

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