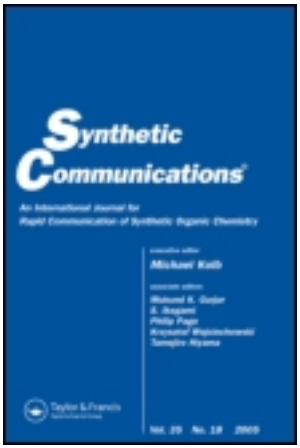

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REACTIONS OF 2-SUBSTITUTED EPICHLOROHYDRINS

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Abstract: 2-Substituted epichlorohydrins have been synthesized by starting with 1,2-dichloro acetone and various alkyl and aryl halides via dichlorohydrins followed by cyclization. The reactive 2-substituted epichlorohydrins were subjected to nucleophilic attacking of azide and cyanide ions to afford corresponding β-azido alcohols and α,β-unsaturated nitriles.

Epichlorohydrins have emerged as valuable synthons for organic synthesis. Exploration into the reactivity of epichlorohydrins has been a highly active area of research[1-6]. Epichlorohydrins are very simple compounds for which a wide variety of different substitution patterns can be generated[7]. In general, transformation of

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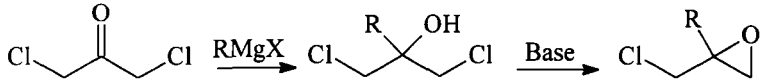
epichlorohydrin to other functional groups happens by ring opening of the more reactive epoxide group. Sterically less hindered carbon of epoxide undergoes nucleophilic attack by various nucleophiles.

The first step of our study was the use of Grignard reaction to introduce various alkyl and aryl substituents into dichloro acetone to afford corresponding dichlorohydrins **1**. It was observed that the addition of Grignard reagent to the carbonyl group of dichloro acetone interfere with the substitution of α-halogens, presumably due to the high electrophilicity of the carbon atom of the carbonyl unit. The conversion of the dichlorohydrins **1** to substituted epichlorohydrins **2** was carried out with base such as $Ca(OH)_2$. As shown in Scheme 1 and Table1 the formation of alkoxide ion followed the ring closure reaction yielded 2-substituted epichlorohydrins .



1 a-h **2 a-h**

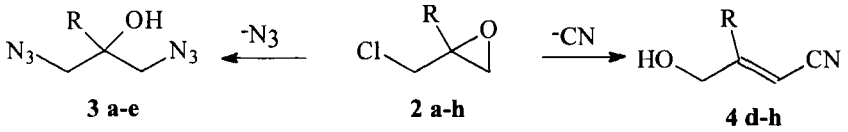
Scheme 1

As shown in Scheme 2 and Table 2, we tried to open oxirane ring by using NaN_3 in a nucleophilic ring opening reaction manner to obtain azido alcohols. Epoxides react with NaN_3 to give β-azido alcohols. The azido alcohols are very valuable

Table 1

R	Product 1	Yields (%)	Product 2	Yields (%)
Methyl	a	97	a	62
Ethyl	b	98	b	64
i-Propyl	c	79	c	65
Butyl	d	91	d	63
Phenyl	e	95	e	93
Biphenyl	f	86	f	94
Benzyl	g	80	g	75
Styryl	h	74	h	83

precursors for the syntheses of various biologically active compounds[8]. This result arises from the fact that azido alcohols are converted easily to aziridines which are significant compounds for the synthesis of amino alcohols and amino acids.The reaction of 2-substituted epichlorohydrins **2** with two equivalents of sodium azide in dioxane gave diazido alcohol **3** in good yields. When the same reaction was carried out in the presence of 1 equivalent of sodium azide, a mixture of diazido alcohols and mono azido derivatives would form. From the spectroscopic data, we infer that the one azide ion attacks from the less substituted carbon atom of epoxide ring and second azide group replaces with chlorine. In ^{1}H-NMR spectrum the characteristic peak from CH_2N_3 protons of diazido alcohols appears as singlet at 3.35 ppm and ir spectrum shows a strong peak at 2050 cm^{-1} for azido group.



3 a-e **2 a-h** **4 d-h**

Scheme 2

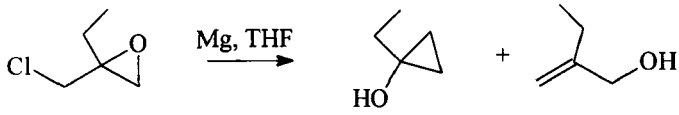
Table 2

R	Product 3	Yields (%)	Product 4	Yields (%)
Methyl	a	82	-	
Ethyl	b	89	-	
i-Propyl	c	79	-	
Butyl	d	74	d	75
Phenyl	e	74	e	78
Biphenyl	-		f	65
Benzyl	-		g	72
Styryl	-		h	76

We have also tried to open epoxide ring with NaCN. α,β-Unsaturated nitriles are very important precursors for the synthesis of a wide variety of biologically active compounds. We have recently defined a new procedure for unsaturated nitriles by the ring opening of epichlorohydrins with cyanide. Johnson and his coworkers have synthesized 3-cyanoallylic alcohols as by products in the synthesis of 3-hydroxyglutaronitriles[9]. The reaction of 2-substituted epichlorohydrins with

NaCN was taken to synthesize 3-hydroxy-α,β-unsaturated nitriles which are synthetically important Michael acceptors. In addition to being usefull precursors, α,β-unsaturated nitriles obtained in this study can be further functionalized at the γ-position. When the reaction was carried out at room temperature, we observed 3-substituted-3-hydroxyglutaronitriles and 3-cyanoallylic alcohols in 3:1 ratio, respectivelly. By increasing the temperature of the reaction medium for satisfying selectivity, the yield of 3-cyanoallylic alcohols drastically increased. In this reaction, various 2-substituted epichlorohydrins **2** were treated with NaCN to synthesize 3-cyanoallylic alcohols **4**.During the course of these reactions, nitrile always reacts with the less hindered carbon of epoxide unit as expected in a S_N2 mechanism.

Another interesting reaction type of 2-substituted epichlorohydins was developed to form substituted cyclopropanols (homoenolate precursors) They are used for numerous synthetic and mechanistic studies. Several methods have been reported for the synthesis of cyclopropanols[10-12]. The reaction of 2-chloromethyl-2-ethyloxirane **2b** with Mg in THF under reflux should have given the 1-ethylcyclopropanol **5**, via the intramolecular Grignard reaction through our estimations. From spectroscopic data we understood that we obtained two different products. The crude ^{1}H-NMR and IR spectra of the product showed that not only did we get 1-ethylcyclopropanol **5**, but also we obtained 2-methylene-1-butanol (2-ethylallyl alcohol) **6** shown in Scheme 3. The same procedure was



2b **5** **6**

Scheme 3

applied for the other epichlorohydrins and the corresponding cyclopropanols and allyl alcohols were obtained as a mixture.

Experimental Section:

The ^{1}H-NMR spectra were taken on a Bruker AC 80 MHz FT-NMR spectrometer. Chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Spin multiplicities were reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The infrared spectra (IR) were recorded on a Nicolet 510 FT-IR spectrometer.Elemental analyses were performed at the Middle East Technical University Analysis Center.

Flash column chromatography was performed using thick-walled glass columns and *flash grade* silica (Macherey-Nagel Kieselgel 60-400 mesh). Routine thin layer chromatography (TLC) was affected by using precoated 0.25-mm silica gel plates purchased from Whatman. The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. Solvents and reagents used were reagent grade.

General Procedure I: Preparation of Dichlorohydrins

1-Chloro-2-(chloromethyl)-2-propanol (**1a**): To the solution of Mg turnings (1.6 g, 65.0 mmol) in diethyl ether (30.0 ml) was added dropwise a solution of methyl iodide (7.0 g, 65.0 mmol) in dry ether (5.0 ml) from dropping funnel over a period of 30 min. The mixture was refluxed until all magnesium turnings disappeared. Then the reaction mixture was cooled to 0 °C and to this reaction mixture a solution of dichloroacetone (8.3 g, 65.0 mmol) in dry ether (20.0 ml) was added dropwise for a period of 1 h. The resultant mixture was further stirred for 30 min. at the same temperature, and then refluxed for 3 h. After reflux, mixture was allowed to cool to room temperature and hydrolyzed with saturated ammonium chloride solution (20.0 ml) and 1 N HCl (5.0 ml), respectively. The resulting mixture was extracted with diethyl ether (3 x 25 ml). The organic solution was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography using 5:1 *n*-hexane/ethyl acetate as the eluent to give the product 1a (97 % yield); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 1.40 (s, 3H, CH_3), 2.42 (broad s, 1H, OH), 3.63 (s, 4H, CH_2Cl); IR (neat) ν_{max} 3500, 2980-2920 cm^{-1}.

1-Chloro-2-(chloromethyl)-2-butanol (**1b**) was prepared in 98 % yield as above procedure (general procedure I); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 0.95 (t, 0.95 (t, J=7 Hz, 3H, CH_3), 1.65 (q, J=7 Hz, 2H, CH_2), 2.30 (broad s, 1H, OH), 3.40-3.70 (m, 4H, CH_2Cl); IR (neat) ν_{max} : 3500, 2980-2920 cm^{-1}.

1-Chloro-2-(chloromethyl)-3-methyl-2-butanol (**1c**) was prepared in 79 % yield as above procedure (general procedure I); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 1.05 (d, J=7 Hz, 6H, CH_3), 1.60-1.80 (m, 1H, CH), 2.30 (broad s, 1H, OH) (D_2O exchange), 3.60-3.80 (m, 4H, CH_2Cl); IR (neat) ν_{max} : 3500, 2900-2980 cm^{-1}.

1-Chloro-2-(chloromethyl)-2-hexanol (**1d**) was prepared in 91 % yield as above procedure (general procedure I); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 0.95 (t, J=7 Hz, 3H, CH_3), 1.50-1.90 (m, 6H, CH_2), 2.25 (broad s, 1H, OH), 3.50-3.62 (m, 4H, CH_2Cl); IR (neat) ν_{max} : 3500, 2980-2900 cm^{-1}.

1,3-Dichloro-2-phenyl-2-propanol (**1e**) was prepared in 95 % yield as above procedure (general procedure I); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 3.00 (s, 1H, OH), 3.90 (s, 2H, CH_2Cl), 7.2-7.6 (m, 5H, C_6H_5), IR (neat) ν_{max} : 3500, 2980, 3030, 710 cm^{-1}.

2-Biphenyl-1,3-dichloropropan-2-ol (**1f**) was prepared in 86 % yield as above procedure (general procedure I); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 3.00 (s, 1H, OH), 3.80 (d, 2H, CH_2), 4.00 (d, 2H, CH_2), 7.2-7.7 (m, 9H, biphenyl); IR (neat) ν_{max} : 3500, 2980 cm^{-1}.

2-Benzyl-1,3-dichloropropan-2-ol (**1g**) was prepared in 80 % yield as above procedure (general procedure I); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 2.90 (s, 2H, CH_2),

3.40 (s, 1H, OH), 3.70 (s, 2H, CH_2), 3.90 (s, 2H, CH_2), 7.00-7.40 (m, 5H, C_6H_5); IR (neat) ν_{max} : 3500, 2990, 3150, 1620 cm^{-1}.

1,1 Dichloromethyl-3-phenylprop-3-en-1-ol (**1h**) was prepared in 74 % yield as above procedure (general procedure I); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 2.70 (s, 1H, OH), 3.70 (s, 4H, CH_2), 6.30 (d, J=15 Hz, 1H, CH), 6.90 (d, J=15 Hz, 1H, CH), 7.20-7.50 (m, 5H, C_6H_5); IR (neat) ν_{max} : 3500, 2990, 710, 960 cm^{-1}.

General Procedure II: Preparation of 2-Substituted Epichlorohydrins

2-Chloromethyl-2-methyloxirane (**2a**): To the solution of calcium hydroxide (1.9 g, 26.2 mmol) in water (13.4 ml) was added 1-chloro-2-(chloromethyl)-2-propanol (5.0 g, 35.0 mmol). The resulting mixture was stirred at 50-55 °C for 6 h. Then, the reaction mixture was allowed to cool to room temperature and neutralized with 1 N HCl. The resulting mixture was extracted with diethyl ether (3 x 25 ml). The combined organic layer was dried over $MgSO_4$. Final purification was achieved by flash column chomatography using 5:1 *n*-hexane/ethyl acetate as the eluent to yield 2-chloromethyl-2-methyloxirane (2.3 g, 62 %). ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 1.20 (s, 3H, CH_3), 2.80 (s, 2H, CH_2O), 3.45-3.55 (m, 2H, CH_2Cl); IR (neat) ν_{max} : 3050-2990 cm^{-1}.

2-Chloromethyl-2-ethyloxirane (**2b**) was prepared in 64 % yield as above procedure (general procedure II); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 0.95 (t, J=7 Hz,

3H, CH_3), 1.80 (q, J=7 Hz, 2H, CH_2), 2.75 (s, 2H, CH_2O), 3.25-3.75 (m, 2H, CH_2Cl); IR (neat) ν_{max} : 3050-2990 cm^{-1}.

2-Chloromethyl-2-isopropyloxirane (**2c**) was prepared in 65 % yield as above procedure (general procedure II); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 0.91-1.50 (m, 6H, CH_3), 1.63-1.95 (m, 1H, CH), 2.75 (s, 2H, CH_2O), 3.55-3.75 (m, 2H, CH_2Cl); IR (neat) ν_{max} : 3050-2990 cm^{-1}.

2-Butyl-2-(chloromethyl)oxirane (**2d**) was prepared in 63 % yield as above procedure (general procedure II); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 0.97 (t, J=7 Hz, 3H, CH_3), 1.65-2.00 (m, 6H, CH_2), 2.75 (s, 2H, CH_2O), 3.55-3.80 (m, 2H, CH_2Cl); IR (neat) ν_{max} : 3050-2990 cm^{-1}.

2-Chloromethyl-2-phenyl oxirane (**2e**) was prepared in 93 % yield as above procedure (general procedure II); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 2.80 (d, J=5 Hz, 1H, CH_2), 3.10 (d, J=5 Hz, 1H, CH_2), 3.70 (d, J=12 Hz, 1H, CH_2), 4.00 (d, J=12 Hz, 1H, CH_2), 7.10-7.50 (m, 5H, C_6H_5); IR (neat) ν_{max} : 3050, 2990, 1610, 1450, 1250, 710 cm^{-1}.

2-Biphenyl-2-chloromethyl oxirane (**2f**) was prepared in 94 % yield as above procedure (general procedure II); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 2.90 (d, J=4 Hz, 1H, CH_2), 3.20 (d, J=4 Hz, 1H, CH_2), 3.80 (d, J=11 Hz, 1H, CH_2), 4.20 (d, J=11

Hz, 1H, CH_2), 7.20-7.80 (m, 9H, biphenyl); IR (neat) ν_{max} : 2980, 1750, 1450, 1250 cm^{-1}.

2-Benzyl-2-chloromethyl oxirane (**2g**) was prepared in 75 % yield as above procedure (general procedure II); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 2.30-3.90 (m, 6H, CH_2), 7.10-7.60 (m, 5H, C_6H_5); IR (neat) ν_{max} : 2850, 1610, 1450, 1260, 1050, 710 cm^{-1}.

2-Chloromethyl-2-styrene oxirane (**2h**) was prepared in 83 % yield as above procedure (general procedure II); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 2.90 (d, J=5 Hz, 1H, CH_2), 3.10 (d, J=5 Hz, 1H, CH_2), 3.70 (s, 2H, CH_2), 6.20 (d, J=16 Hz, 1H, C=CH), 6.80 (d, J=16 Hz, 1H, C=CH), 7.10-7.60 (m, 5H, C_6H_5); IR (neat) ν_{max} : 3032, 2940, 1268, 750 cm^{-1}.

General Procedure III: Preparation of Diazido Alcohols

1-Azido-2-(azidomethyl)-2-butanol (**3b**): To the solution of 2-chloromethyl-2-ethyloxirane (0.5 g, 3.7 mmol) in dioxane (20 ml) was added dropwise a solution of sodium azide (NaN_3, 0.3 g, 4.8 mmol) in water (0.8 ml) from a dropping funnel under reflux. Refluxing continued for sixteen hours. After reflux, mixture was cooled down and extracted with ether (3 x 25 ml). The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 0.5 g (89 %) of 1-azido-2-(azidomethyl)-2-butanol. ^{1}H-NMR (80

MHz, $CDCl_3$) δ: 0.93 (t, J=7 Hz, 3H, CH_3), 1.55 (q, J=7 Hz, 2H, CH_2), 2.08 (broad s, 1H, OH), 3.55 (s, 4H, CH_2N_3); IR (neat) ν_{max} : 3500, 2950-2800, 2050 cm^{-1}. Anal. calc. for $C_5H_{10}N_6O$: C, 35.29; H, 5.92; N, 49.38. Found: C, 35.56; H, 5.98; N, 49.51.

1-Azido-2-(azidomethyl)-2-hexanol (**3d**) was prepared in 74 % yield as above procedure (general procedure III); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 0.90 (t, J=7 Hz, 3H, CH_3), 1.10-1.80 (m, 6H, CH_2), 2.75 (s, 1H, OH), 3.30-3.80 (m, 4H, CH_2N_3); IR (neat) ν_{max} : 3500, 2950-2850, 2100 cm^{-1}. Anal. calc. for $C_7H_{14}N_6O$: C, 42.41; H, 7.12; N, 42.40. Found: C, 42.49; H, 7.03; N, 42.46.

1,3-Bis(azido)-2-phenyl-2-propanol (**3e**) was prepared in 74 % yield as above procedure (general procedure III); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 3.15 (broad s, 1H, OH), 3.60 (s, 4H, CH_2N_3), 7.20-7.60 (m, 5H, C_6H_5); IR (neat) ν_{max} : 3500, 3000-2850, 2100 cm^{-1}. Anal. calc. for $C_9H_{10}N_6O$: C, 49.54; H, 4.62; N, 38.51. Found: C, 49.50; H, 4.59; N, 38.55.

General Procedure IV: Preparation of α,β-Unsaturated Nitriles

1-Cyano-2-butyl-1-propen-3-ol (**4d**): A solution of 2-chloromethyl-2-butyl oxirane (.5 g, 36.0 mmol) and sodium cyanide (1.8 g, 36.0 mmol) in a 1:1 mixture of ethyl alcohol/water (0.8 ml) was refluxed. The progress of the reaction was monitored by routine TLC until the oxirane was consumed. The resulting mixture

was washed with 1N HCl (20 ml), and then extracted with ether (3 x 25 ml). The combined organic layer was dried over $MgSO_4$. The final purification by preparative TLC afforded 3.75 g (75 %) of **4d**. ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 0.80-1.10 (t, J=6 Hz, 3H, CH_3), 1.10-2.20 (m, 6H, CH_3), 4.30 (d, 2H, CH_2), 5.50 (t, 1H, C=CH); IR (neat) ν_{max} : 3500, 2980, 2100 cm^{-1}. Anal. calc. for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.01; H, 9.37; N, 10.12.

1-Cyano-2-phenyl-1-propen-3-ol (**4e**) was prepared in 78 % yield as above procedure (general procedure IV); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 2.30 (s, 1H, OH), 4.50 (d, 2H, CH_2), 5.80 (t, J=2 Hz, 1H, CH), 7.50 (m, 5H, C_6H_5); IR (neat) ν_{max} : 3500, 3030, 2850, 2260 cm^{-1}. Anal. calc. for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.53; H, 5.75; N, 8.74.

2-Biphenyl-1-cyanoprop-1-en-3-ol (**4f**) was prepared in 65 % yield as above procedure (general procedure IV); ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 2.20 (s, 1H, OH), 4.60 (d, 2H, CH_2), 5.80 (t, J=2 Hz, 1H, CH), 7.20-7.70 (m, 9H, biphenyl); IR (neat) ν_{max} : 3500, 3030, 2990, 2260 cm^{-1}. Anal. calc. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.61; H, 5.51; N, 5.90.

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