

THE SYNTHESIS OF 2-SUBSTITUTED  
EPICHLOROHYDRINS AND THEIR REACTIONS

Master's Thesis

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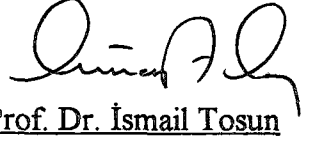
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*To my mother...*

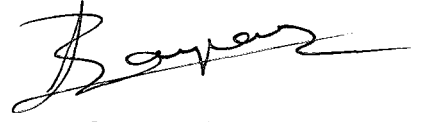
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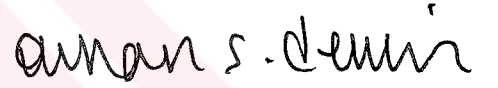
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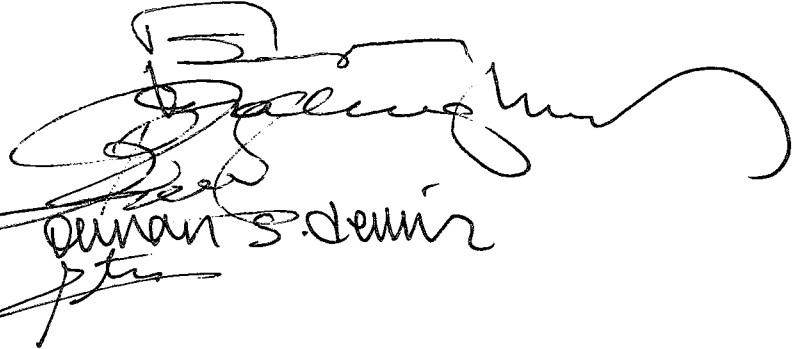
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## ABSTRACT

### THE SYNTHESIS OF 2-SUBSTITUTED EPICHLOROHYDRINS AND THEIR REACTIONS

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A new synthetic method was developed for the synthesis of diazido alcohols, 1-substituted cyclopropanols and 2-substituted allylic alcohols. Azido alcohols are used for the synthesis of amino alcohols, which both are used as drugs and are important starting materials for many drugs, and amino acids. Cyclopropanols and allylic alcohols are of great importance in synthetic organic chemistry since they are transformed into homoenolate derivatives and they are interesting starting materials.

In this work, Grignard reaction of dichloroacetone with different alkyl and aryl halides yielded corresponding dichlorohydrins. Under basic reaction condition, resultant dichlorohydrins were converted to 2-substituted epichlorohydrins with quaternary carbon atom which are versatile compounds for a lot of transformations. Then, 1-substituted cyclopropanols and 2-substituted allylic

alcohols were obtained as a mixture via intramolecular rearrangement of the Grignard reagents of the epichlorohydrins. Nevertheless, this mixture could not be separated. So, for this part of the work, a new method which either enables to separate the products or to convert cyclopropanol to allyl alcohol is required. Ring-opening reaction was carried out with sodium azide and epichlorohydrins to obtain diazido alcohols.

Key words: Dichlorohydrins, Epichlorohydrins, Cyclopropanols, Allylic alcohols, Diazido alcohols.

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## ÖZ

### 2-SUBSTİTÜE EPİKLOROHİDRİNLERİN SENTEZİ VE REAKSİYONLARI

ÖZGÜL, Emine

Yüksek Lisans Tezi, Kimya Anabilim Dalı

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Diazido alkollerin, 1-substitüe siklopropanollerin ve 2-substitüe allilik alkollerin sentezlenmesi için yeni bir metot geliştirilmiştir. Diazido alkoller, hem ilaç olarak kullanılan hem de ilaçlar için önemli başlangıç maddesi olan amino alkollerin, ve amino asitlerin sentezinde kullanılmaktadır. Siklopropanoller ve allilik alkoller, homoenolat türevlerine çevrilmeleri ve ilginç başlangıç maddesi olma özellikleri bakımından sentetik organik kimyada önemli bir yere sahiptirler.

Bu çalışmada, dikloroasetonun çeşitli alkil ve aril halojenürlerle olan Grignard tepkimeleri diklorohidrin yapıları oluşturmuştur. Bazik tepkime koşulları altında, elde edilen diklorohidrinler, bir çok transformasyon için çok kıymetli bileşikler olan epiklorohidrinlere dönüştürülmüştür. Daha sonra, epiklorohidrinlerin Grignard reaktiflerinin rearanjmanı sonucu 1-substitüe siklopropanoller ve 2-substitüe allilik alkoller karışım olarak elde edilmiştir. Fakat, bu karışım

ayrılmamıştır. Dolayısıyla, çalışmanın bu kısmı için ürünlerin ayrılmasına olanak veren ya da sikloprapanolü allil alkole çeviren yeni bir metot gerekmektedir. Epiklorohidrinlerin sodyum azit ile halka açılma reaksiyonları incelenmiş ve bu reaksiyonlarla da diazido alkoller elde edilmiştir.

**Anahtar Kelimeler:** Diklorohidrinler, Epiklorohidrinler, Siklopropanoller, Allilik alkoller, Diazido alkoller.

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## CHAPTER I

### INTRODUCTION

#### 1.1. The Importance of Epoxides and 2-Substituted Epichlorohydrins.

##### 1.1.1. The Dichlorohydrins.

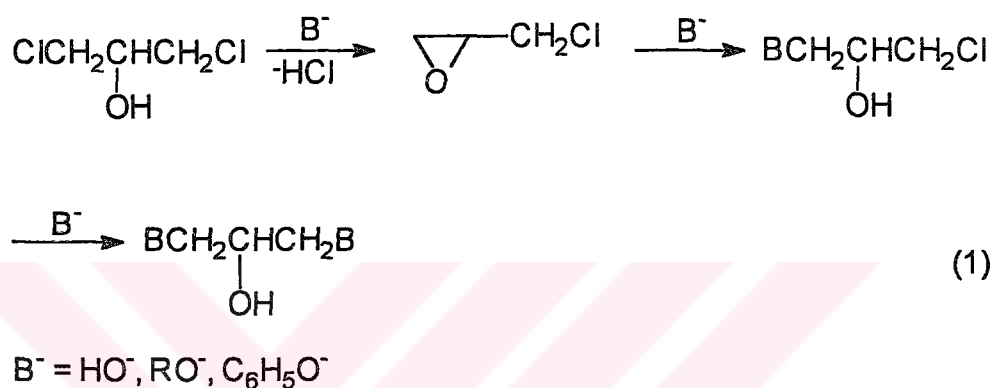
The chlorohydrins containing one or more chlorine atoms and one or more hydroxyl groups are important poly functional compounds in the synthesis of many different biologically active materials.

The chlorohydrins are slightly unstable. Chemically, they behave as either alcohols or chlorides and show the typical reactions of these compounds.

Chlorohydrins are generally prepared by addition of hypochlorous acid to olefins (chlorohydrination) or by reaction of hydrochloric acid with epoxides or glycols. The addition of the chloride occurs preferentially at the least substituted carbon.

Reactions of dichlorohydrins can be divided into three categories: reactions involving both the chlorine and hydroxyl groups, and reactions involving either the hydroxide or the chlorine.

Many reactions involving both hydroxyl and chlorine are base catalyzed and epichlorohydrin is formed as the intermediate. In fact, most of the reactions can be more conveniently carried out with epichlorohydrin (1).



The hydroxyl group of the dichlorohydrin can undergo the typical reactions of alcohols, such as esterification with organic acids or acid chlorides.

The chlorine group reacts under proper conditions with sodium azide to form mono- and diazido derivatives.

Epichlorohydrin (1-chloro-2,3-epoxypropane) is a cyclic three-membered ether (oxirane). It takes great importance since it is the only chlorohydrin sold on a large scale, and it is an important starting material by the synthesis of  $\beta$ -blockers. It is easily prepared from glycerol 2,3-dichlorohydrin and its reactions are similar to glycerol dichlorohydrins.

Epoxidation is carried out by the reaction of peracids and hydrogen peroxide with olefinic and aromatic double bonds. Oxiranes may also be formed by an internal  $S_N2$  reaction of a chlorohydrin [1, 2].

"If carbonyl compounds have been said to be 'virtually the backbone of the organic synthesis', the epoxides correspond to at least 'one of the main muscles' ". This sentiment expressed by Seebach [3] shows the importance of epoxides in organic synthesis. Indeed, the literature confirms that much effort has been expended on the investigation of epoxide chemistry in the past. More importantly, it indicates that the synthesis of natural products via epoxide-containing intermediates are of great interest.

Epoxides are easily prepared from a variety of compounds. In addition, epoxides are easily opened under a wide range of conditions. One very favorable aspect of epoxide-opening reactions is that they are usually stereospecific, proceeding with inversion of configuration at the site of ring-opening via an  $S_N2$  mechanism. For this reason, methods for the highly enantioselective synthesis of epoxides would be quite valuable [3].

The distinguishing characteristic of the cyclic ether is that the ring can be opened in a single bimolecular reaction, which involves no preequilibrium step, to produce a good yields of products. The rates of the ring-opening reactions are related to the stabilities of the anions produced ( $-S^- > -O^- > -N^-$ ).

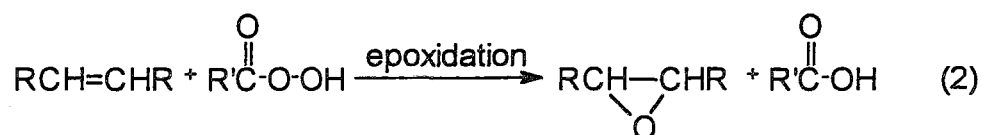
## 1.2. The Synthesis of Epoxides and 2- Substituted Epichlorohydrins and Their Reactions.



### 1.2.1. Classical Methods.

The majority of epoxide synthesis involve the standard reagents: a peracid attacking an olefin and a ring closure of a halohydrin.

#### 1) A Peracid Attacking An Olefin:



In this reaction the peroxy acid (peracid) transfers an oxygen atom to the alkene. The addition of oxygen to double bond in an epoxidation reaction is a *syn* addition.

#### 2) A Ring Closure of a Halohydrin:

The action of alkali on such a chlorohydrin results in the elimination of hydrogen chloride and the formation of an  $\alpha$ -oxide ring (3).

### 1.2.2. Special Reagents.

A large number of special reagents have been applied to the synthesis of epoxides such as:

- Wittig Reagent
- Phosphorus Triamide
- Carbenes
- Sulfonium and Oxosulfonium Ylides
- Nitric Acid
- Oxygen

### 1.2.3. Reactions Between $\alpha$ -Oxides and Inorganic Acids and Their Salts.

Ethylene oxide and its homologues readily react with hydrohalic acids to form halohydrins (4).

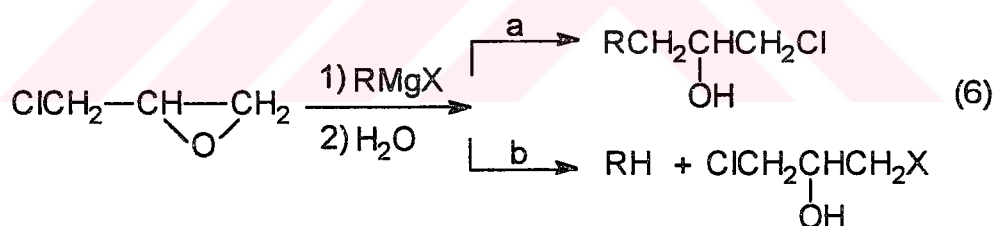
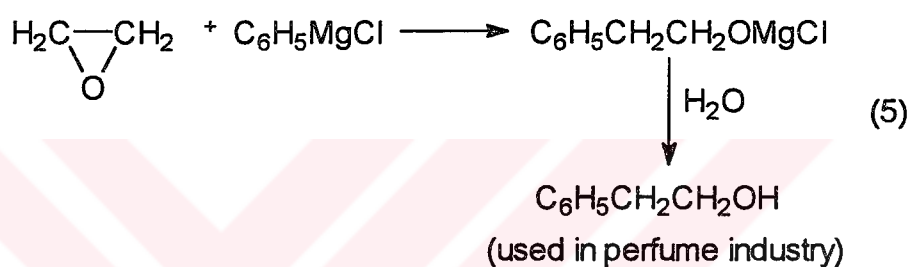


Asymmetrical epoxides combine with HCl so that the hydroxyl group is formed at the least hydrogenated carbon atom of the oxide ring.

The reactions of olefin oxides with ammonia and amines are of great interest in view of the fact that many of the products are widely used in many different fields. This is especially true of ethanol amines (hydroxy ethylamines).

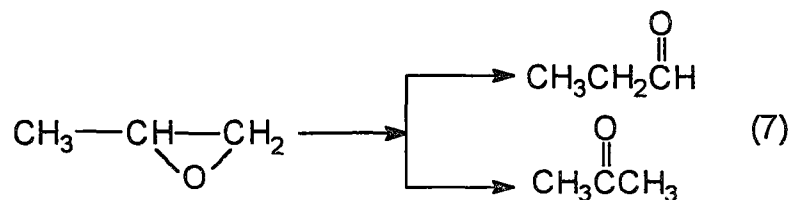
Ethanol amines can be used for the preparation of photographic emulsions, as wetting agents, as accelerators and antioxidants in the rubber industry, as antifreeze for the radiators of airplane and automobile engines, for the production of certain chemico-pharmaceutical preparations and in the dye industry. Furthermore, ethanolamine soaps are recommended for use in the perfume, textile, leather industries and pesticides in agriculture.

#### 1.2.4. Reactions of $\alpha$ -Oxides With Organometallic Compounds.



#### 1.2.5. Isomerization of $\alpha$ -Oxides.

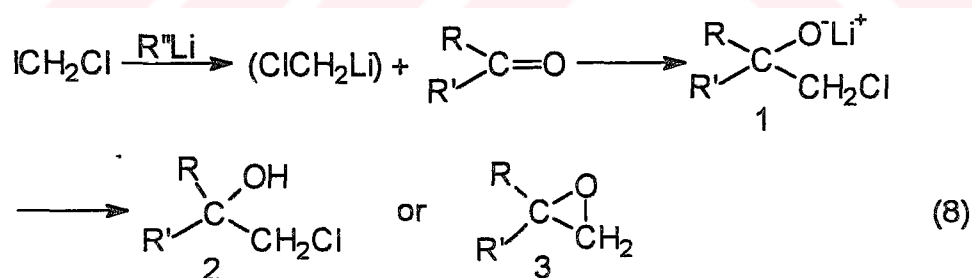
This isomerization process can be used to judge the tendency of radicals to migrate as a function of their influence on one another (7).



It is used in practice in the synthesis of aldehydes or ketones which are difficult to prepare by other methods.

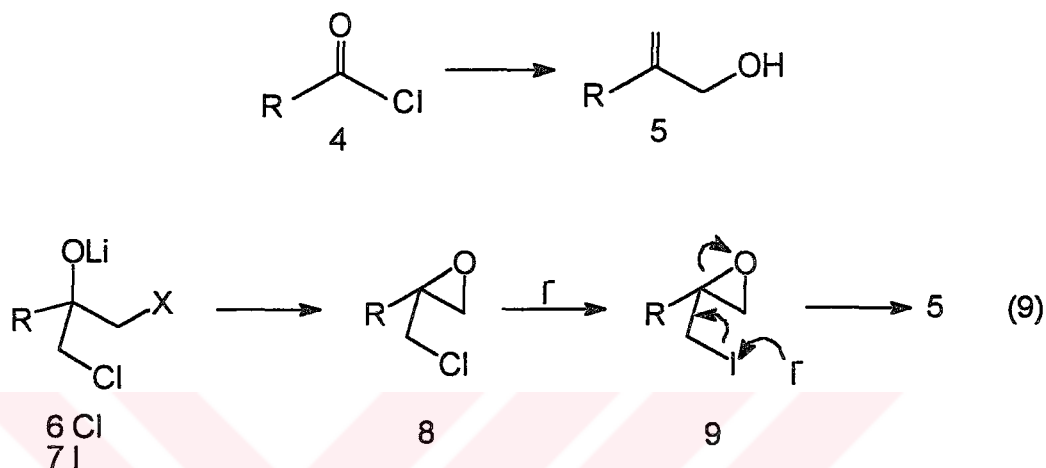
Unsaturated aldehydes, ethers and alcohols are formed as by-products in the isomerization of epoxides [4, 5].

Sadhu and Matteson [6] reported the conversion of aldehydes and ketones to chlorohydrins and oxiranes with (chloromethyl)lithium,  $\text{ClCH}_2\text{Li}$ , generated in situ from iodochloromethane,  $\text{ICH}_2\text{Cl}$  and alkyllithium. Very high yields of chlorohydrins 2 and oxiranes 3 was obtained, and the product depended on whether the lithium alkoxide intermediate 1 is protonated immediately or allowed time to undergo ring closure (8).



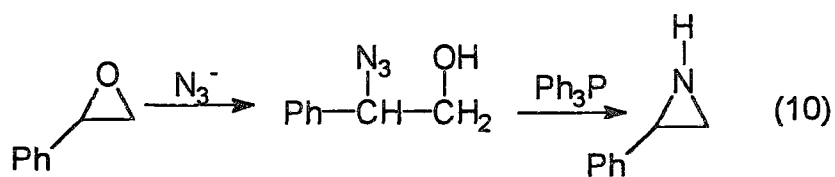
Barluenga et. al. [7, 8] describes a convenient, rapid and versatile procedure for the synthesis of 2-substituted allylic alcohols and epichlorohydrins starting from readily available carboxylic acid chlorides.

Treatment of carboxylic acid chlorides 4 with chloromethyl-lithium generated in situ (1:2 molar ratio) in the presence of lithium iodide leads, after hydrolysis, to the corresponding homologated 2-substituted allyl alcohols 5. When the same reaction is carried out using iodide-free butyl-lithium, instead of methyl-lithium-lithium iodide, 2-substituted epichlorohydrins 8 are formed (9).



### 1.3. The Important Reactions of Epoxides and 2-Substituted Epichlorohydrins With Other Nucleophiles.

Epoxides react with  $\text{NaN}_3$ , with  $\text{HN}_3$  in DMF, or with  $\text{HN}_3$ -  $\text{Et}_3\text{Al}$  to give  $\beta$ -azido alcohols. These reactions are very valuable because they are easily converted to aziridines, and then amino acids [9] (10). For example, aziridines with carboxyl groups are one of the important amino acid precursors.



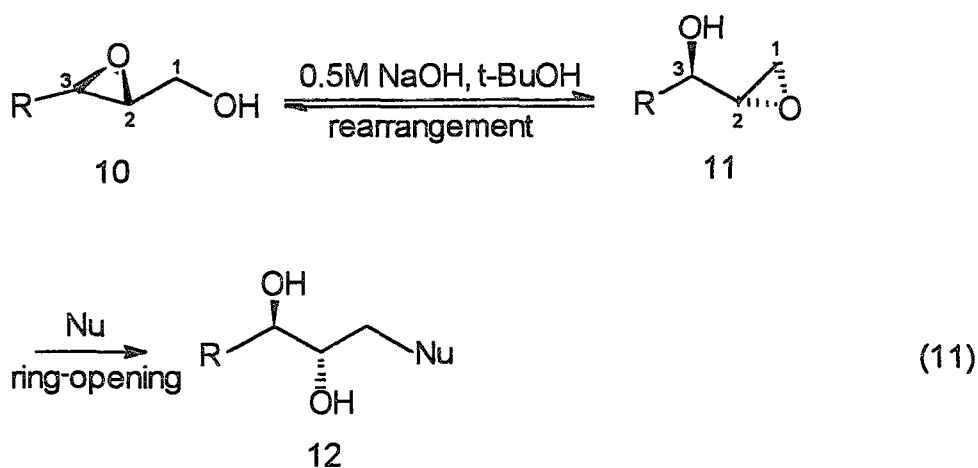
Cleavage of oxirane with hydrazoic acid ( $\text{HN}_3$ ) in DMF was used to synthesize chiral  $\beta$ -hydroxy- $\alpha$ -amino acids. Saito et. al. [10] synthesized erythro- $\beta$ -hydroxy-L-aspartic acid and erythro- $\beta$ -hydroxy methyl-L-serine derivatives in optically pure form from L- and D- tartaric acids.

Iida and his coworkers [11] used  $\text{NaN}_3$  in the synthesis of antibiotic (+)-Nojirimycin and (+)-1-Deoxynojirimycin.

Sharples et. al. [3] studied the selective transformations of 2,3-epoxy alcohols and related derivatives. The regioselectivity ring-opening reactions of 2,3-epoxy alcohols provide convenient access to useful, highly functionalized homochiral molecules.

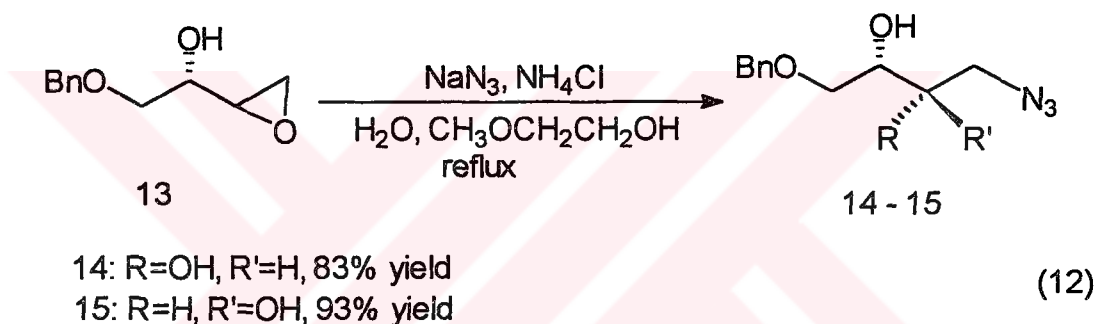
In principle, there are three reactive sites for nucleophilic substitution in a 2,3-epoxy alcohol.

For nucleophilic substitution at C-1 of a 2,3-epoxy alcohol, they used Payne rearrangement-opening reaction (11).

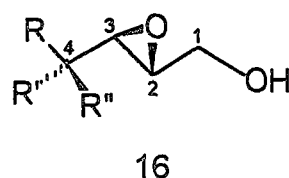


A great advance in the synthetic utility of the Payne rearrangement come with the realization that a nucleophile which is introduced into an equilibrating mixture of epoxy alcohols may react selectively with one of the epoxy alcohols. The rate of reaction of 11 with any nucleophile is expected to be much faster than that of 10 with the same nucleophile, because the C-1 position of 11 is much less hindered than either the C-2 or C-3 position of 10.

They showed that although  $\text{NaN}_3$  is not an effective nucleophile in the rearrangement-opening reaction, it is an excellent nucleophile for the ring-opening of 13 (12).

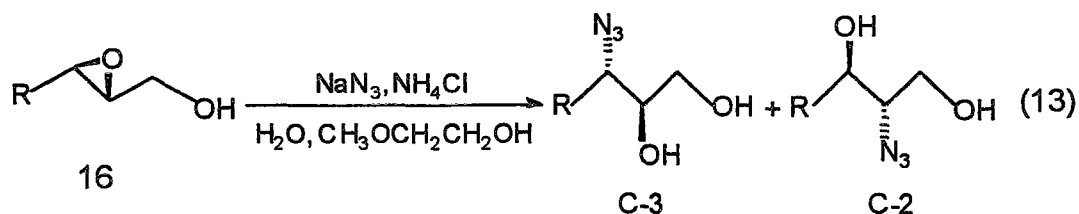


In another study [12], they investigated the ring-opening reactions of 2,3-epoxy alcohols 16 under nonisomerizing conditions.



Nucleophilic substitution of 16 at the C-2 or C-3 positions is not as straightforward because the ring-opening reactions are not always regioselective. Studies show that steric hindrance is not always the only factor to influence the

regioselectivity of epoxy alcohol ring-opening reactions. In addition to steric effects, electronic effects can play an important role in epoxide ring-opening reactions (13).



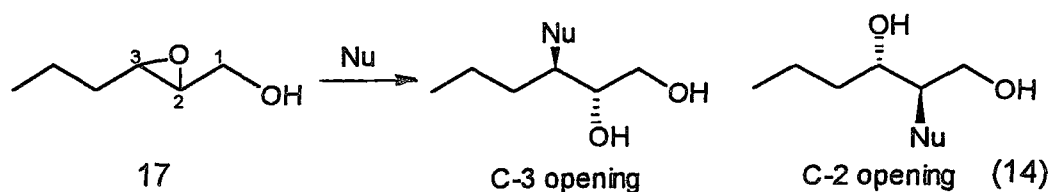
The preference for ring-opening at the C-3 position of simple 2,3-epoxy alcohols occurs in the case of oxygenated 2,3-epoxy alcohols (i.e., 16 ; R=alkoxy, R'=alkyl, R''=H), because in such cases the C-3 carbon bears a substituent that is not only sterically demanding but is also capable of exerting an electron-withdrawing inductive effect.

Electronically, a substituent may exert its effect through resonance or induction or both. Resonance donating substituents (e.g., phenyl, vinyl) promote ring-opening at the proximal carbon atom. But, strong inductive electron-withdrawing substituents (e.g., trifluoromethyl) deter ring-opening at the proximal carbon atom.

In another study, Sharples and his coworkers [13] found that the presence of  $\text{Ti}(\text{O}-i\text{-Pr})_4$  during the openings of 2,3-epoxy alcohol 17 with a variety of nucleophiles markedly increases the rates and regioselectivities of these processes.



They report that coordination of epoxy alcohol to metal alkoxides, especially  $\text{Ti}(\text{OR})_4$ , also greatly facilitates their opening reactions with intermolecular nucleophiles. In addition, in the presence of the metal alkoxide, most of the external nucleophiles show a very strong preference for attack at C-3 of the epoxy alcohol (14).



They studied with amines, alcohols, thiophenol, azide and cyanide as nucleophiles. Azide and cyanide are effective nucleophiles as others under  $\text{Ti}(\text{O-i-Pr})_4$ -mediated conditions. Refluxing 17 in benzene with  $\text{Me}_3\text{SiN}_3$  and  $\text{Ti}(\text{O-i-Pr})_4$  for 3h gave a 74% yield of the azido diols in a C-3 to C-2 ratio of 14/1. They found that when  $\text{Ti}(\text{O-i-Pr})_4$  is omitted, there is no ring opening.

Since the work-up, distillation and storage of epoxides are very difficult, Sharples and his coworkers [14] tried to convert this bad situation into an advantage. They opened the terminal epoxide group in situ without isolation of the unstable epoxy alcohol. By starting from allylic alcohols, they obtained asymmetric epoxides and by in situ opening process, they obtained diols. Their nucleophiles were thiols, secondary amines and phenols.

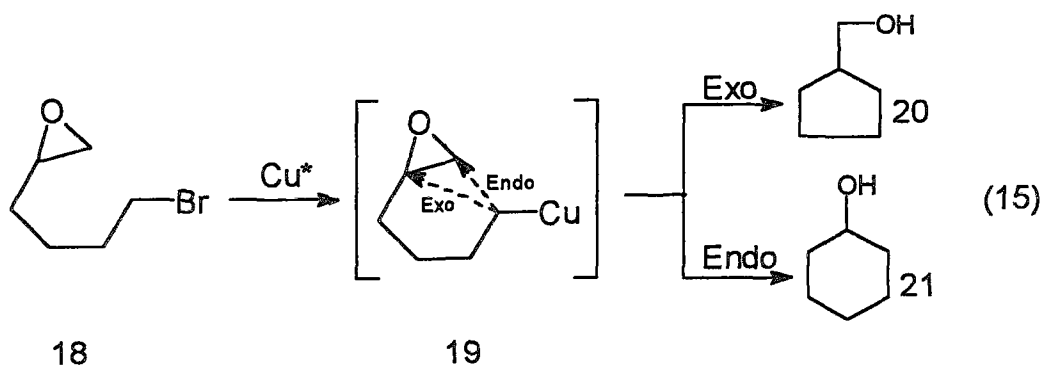
The in situ opening process, not only allows easier handling of the products, but also provides more advanced synthetic intermediates than the parent epoxy alcohols.

Posner and coworkers [15, 16] found that a stirred slurry of commercially available Woelm, 200, neutral (W-200-N) chromatographic alumina (activity "Super I" on the Brockmann scale) catalyzes opening of a very wide variety of epoxides by only a few equivalents of various heteroatom-H (RZ-H) nucleophiles reproducibly and under exceedingly mild conditions (10 min to 1 hour, 25 °C, diethyl ether solvent).

Alumina impregnated with a few equivalents of nucleophiles (alcohols, thiols, benzene selenol, amines and acetic acid) opens epoxides regioselectively at the less substituted epoxide carbon atom and stereospecifically (trans) to give the corresponding  $\beta$ -functionalized alcohols cleanly and in good yields.

As it is often desirable to open an epoxide in the presence of some other functional groups (i.e., chemoselectively), they have established that alcohols, nitriles, ketones, esters and olefins are relatively stable to RZ-H doped alumina for 1 hour at 25 °C.

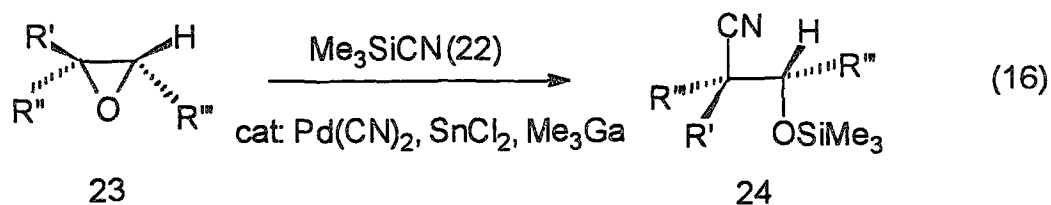
Rieke and coworkers [17, 18] demonstrated that difunctional molecules, containing both an epoxide and a halide, can undergo intramolecular cyclization mediated by the activated copper to generate new carbocycles. For example, treatment of 6-bromo-1,2-epoxyhexane 18 with activated copper in THF -78 °C formed 5,6-epoxyhexylcopper 19 which cyclized upon warming to give a 1:6 mix of 20:21 in 56% yield (15).



Highly reactive copper solutions have been prepared by the lithium naphthalide reduction of copper (I) iodide/trialkylphosphine complexes. These activated copper solutions will react with organic halides under very mild conditions to form stable organocopper reagents.

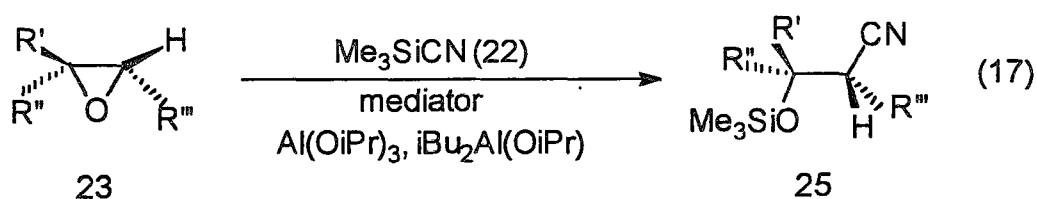
They described the influence of the connecting chain length, substitution pattern, reaction solvent, and CuI/phosphine complex upon the regioselectivity of the intramolecular cyclization.

Imi and coworkers [19] studied the reaction of cyanotrimethylsilane 22 with oxiranes 23, and effects of catalysts and mediators on regioselectivity. Under the catalytic action of Lewis acids  $\text{Pd}(\text{CN})_2$ ,  $\text{SnCl}_2$  or  $\text{Me}_3\text{Ga}$ , 2-trimethylsiloxy isocyanides 24 are prepared from various oxiranes 23 by regioselective attack of isocyanide on the more substituted carbon with inversion of configuration. Reaction at 3° carbon atoms also proceeded stereospecifically (16).



Coordination of Lewis acids to oxygen activates oxiranes 23 by stretching the bond between oxygen and more substituted carbon. Then weakly nucleophilic 22 attacks the more electrophilic site of the activated oxiranes. These factors explain the regio- and stereoselective isocyanosilylation of 23 with 22.

When reaction of 22 with 23 was carried out in the presence of aluminum chloride or aluminum alkoxide, 3-trimethylsiloxy nitriles 25 were obtained exclusively (17).



They claim that this procedure is very useful for the preparation of optically active isocyanides 24 and nitriles 25.

#### 1.4. The Synthesis of Cyclopropanols From 2-Substituted Epichlorohydrins and Their Reactions.

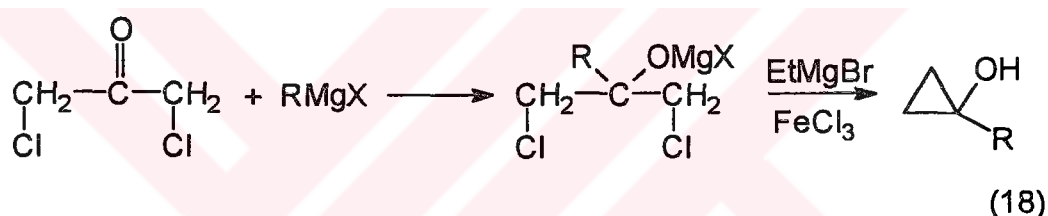
Cyclopropanols are interesting molecules in organic synthesis due mainly to their ability to be transformed into homoenolate derivatives. They are used for numerous synthetic and mechanistic studies.

Several methods are reported for the synthesis of cyclopropanols.

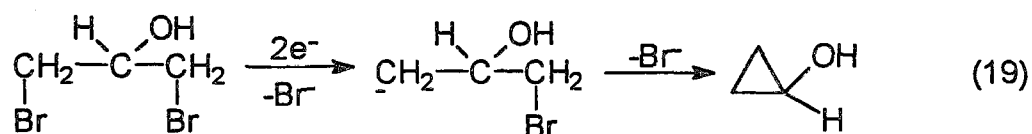
#### 1.4.1. Synthesis From 1,3-Dihalo Compounds.

The simplest method for the synthesis of cyclopropanol is that accidentally discovered by Cottle et. al. [20] which involves the reaction of epichlorohydrin with magnesium bromide, ethylmagnesium bromide, and ferric chloride.

By a modification of this method DePuy and his coworkers [21,22] synthesized 1-substituted cyclopropanols (60% yield). The main precaution to be observed in these reactions is to avoid undue contact of cyclopropanols with acids or with bases in the presence of protic solvents (18).

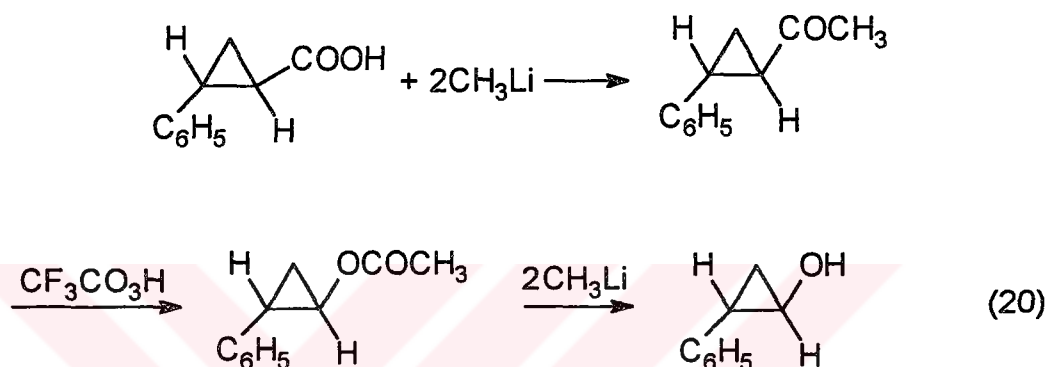


Later, a further modification was done by Gerdil [23]. Dehalogenation is accomplished by an electrochemical process and cyclopropanol is obtained in good yields (19).

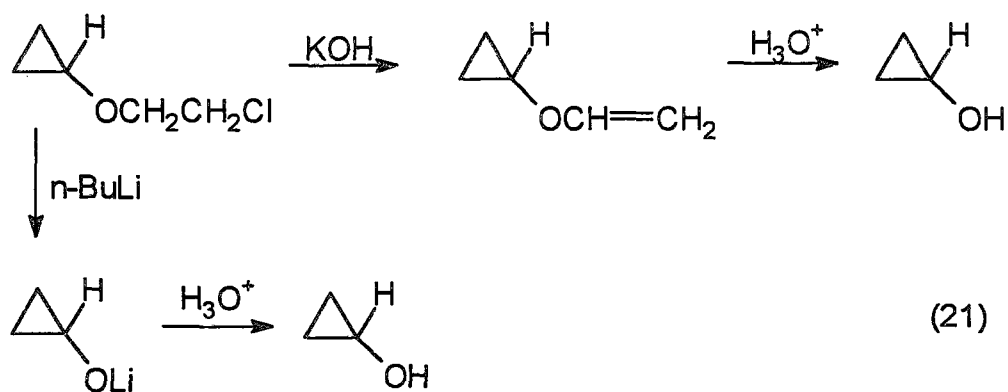


#### 1.4.2. Synthesis by Cleavages of Esters and Ethers.

It was shown that cyclopropyl acetate could be hydrolyzed to give cyclopropanol [24]. The yield is improved if the ester cleavage is performed with lithium aluminum hydride (53%) or, more conveniently by use of methyl lithium. The method has general utility since a wide variety of cyclopropyl acetates are available or accessible from the carboxylic acids. Great caution must be exercised in working up the final reaction to prevent conversion to aldehydes. According to this method, the synthesis of trans-2-phenylcyclopropanol is outlined in (20).

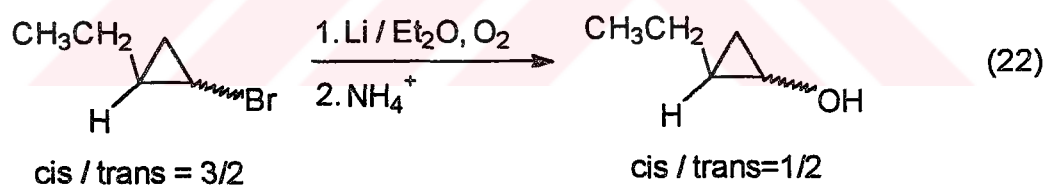


Schöllkopf and his coworkers [25] were the first to develop the ethers as a means of preparing cyclopropanols. The problem inherent in such a synthetic route is to find an R group which can be removed under sufficiently mild conditions that the three-membered ring is not opened concurrently. The first substituent which was found to meet these conditions was the  $\beta$ -chloroethyl group (21).

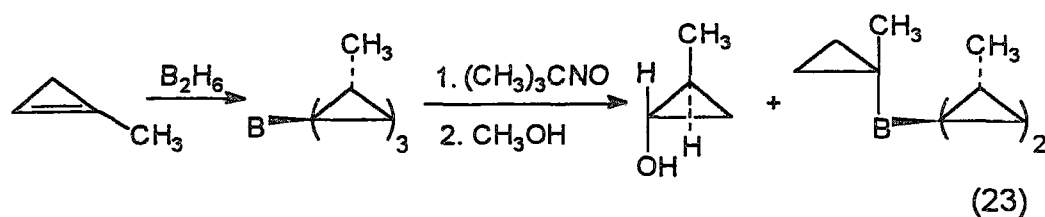


#### 1.4.3. Synthesis by Oxygenation or Oxidation Reactions.

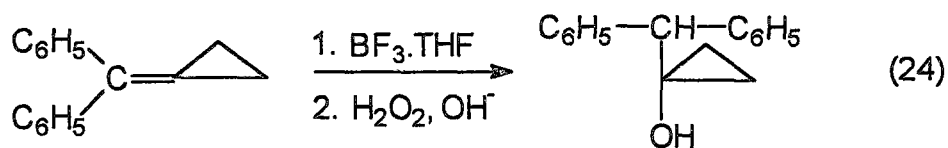
Roberts and Chambers [26] used a different method for the synthesis of the cyclopropanols. Longone and Wright [27] have modified the oxygenation reaction by using cyclopropyllithiums rather than Grignard reagents. The reaction of cyclopropyllithium in this way gives a moderate yield of cyclopropanol, but most other such reactions give good yields of the expected cyclopropanols (22).



Cyclopropanols may be obtained by oxidation of cyclopropylboron compounds, too. Scheme (23) summarizes this procedure.

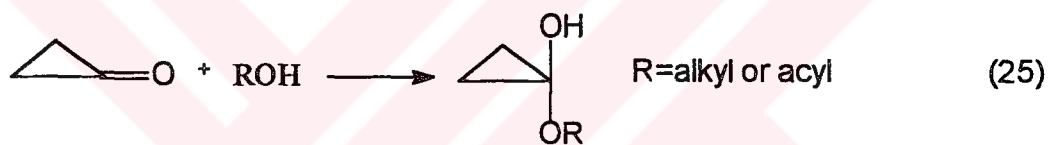


A variation of this procedure involves the addition of  $\text{BH}_3$  to a methylenecyclopropane [29] (24).

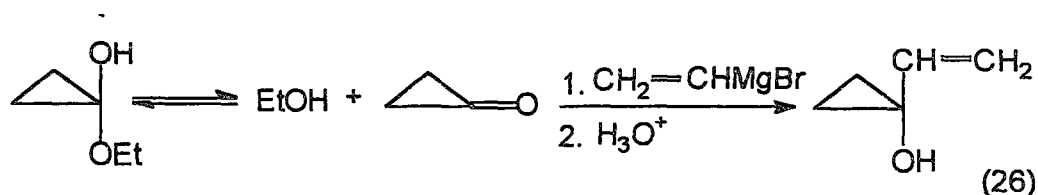


#### 1.4.4. Synthesis From Cyclopropanones and Their Derivatives.

In this method, hemiketals and hemiacetals are formed by direct addition to cyclopropanones (25).



Wasserman and his coworkers [30] prepared 1-substituted cyclopropanols by addition reactions involving cyclopropanone derivatives, especially the hemiketals (26).

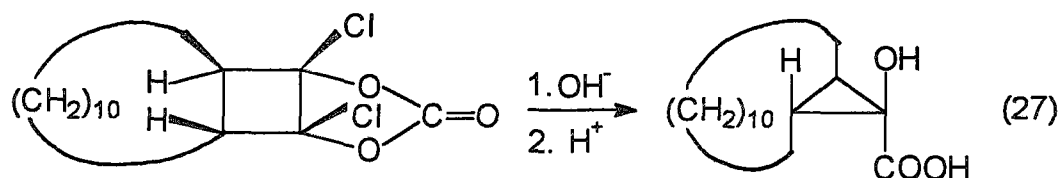


This method depended on a small amount of cyclopropanone present in solution in equilibrium with the hemiketal.

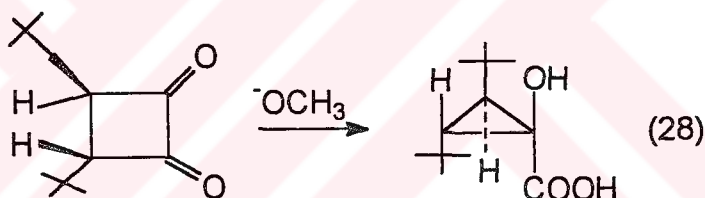


#### 1.4.5. Synthesis by Ring Contraction Reactions.

To prepare 1-substituted cyclopropanols, suitable cyclobutane derivatives was used. Scharf and Klar [31] used a carbonate to prepare an unusual bicyclic system (27).



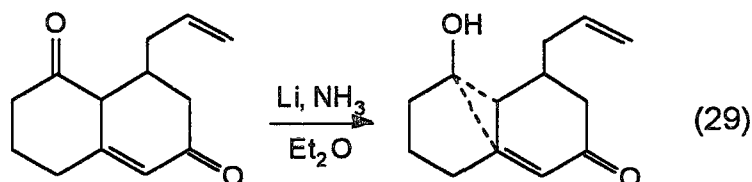
DeGroot and his coworkers [32] showed that *trans*-di-*tert*-butyl-1,2-cyclobutanedione undergoes a benzilic acid type rearrangement when treated with methoxide ion (28).



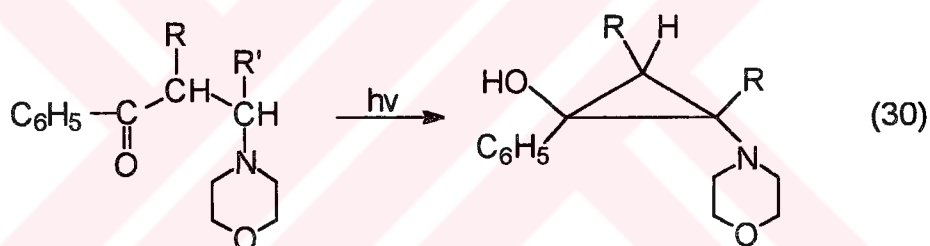
Heine [33] described the conversion of 1,2-cyclobutanedione to 1-hydroxycyclopropane-1-carboxylic acid by the action of either acid or base. Conia and Denis [34] performed the same transformation by using water.

#### 1.4.6. Synthesis by Miscellaneous Other Methods.

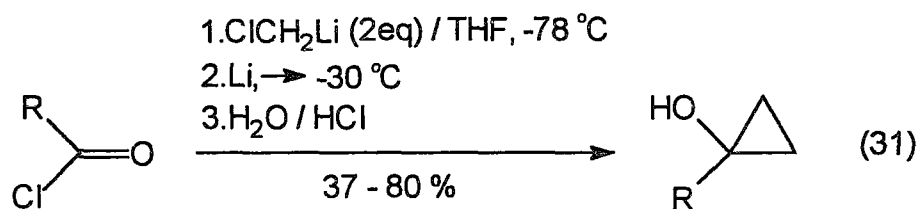
Internal addition of a carbanion to a carbonyl group can, in properly chosen systems, lead to cyclopropanols. Venkataramani and Reusch [35] described the generation of carbanion produced by reduction of an  $\alpha$ - $\beta$ -unsaturated ketone (29).



Several reports have been established involving photochemical routes to cyclopropanols. For example, high yields of cyclopropanols are reported from the photolyses of 3-morpholinopropiophenones in dioxane [36] (30).



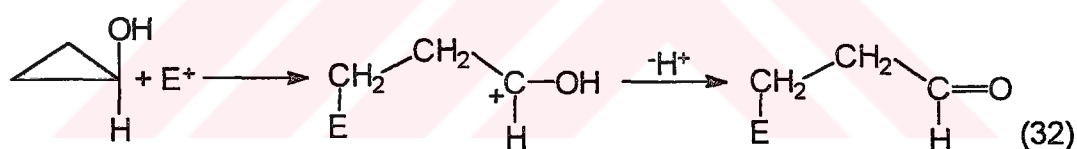
Barluenga and his coworkers [37] described a new method to prepare 1-substituted cyclopropanols starting from carboxylic acid chlorides. Different carboxylic acid chlorides were allowed to react with in situ generated chloromethyl lithium in the presence of lithium bromide at  $-78^\circ\text{C}$  and an excess of lithium powder at temperature ranging between  $-78$  and  $-30^\circ\text{C}$ . Then, the corresponding 1-substituted cyclopropanols were obtained (31).



#### 1.4.7. Ring Opening Reactions of Cyclopropanols and Their Derivatives.

##### 1.4.7.1. Reactions Induced by Electrophiles.

Cyclopropanols undergo ring cleavage reactions very easily when treated by electrophiles (32). They react readily with acids, mercuric salts, and halogenating agents.



Stereochemical studies have shown that the ring-opening reaction with a proton can occur with either retention or inversion of configuration. But generally, it takes place with retention of configuration at the site of electrophilic attack [38, 39].

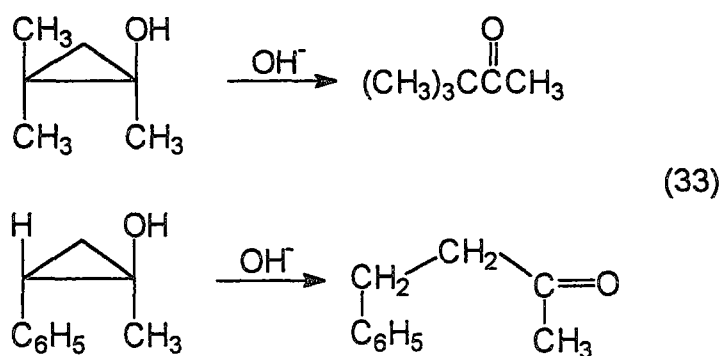
Cyclopropanols and their derivatives react readily with mercuric acetate in either acetic acid or methanol. Attack occurs most readily on the least

substituted bond in the molecule in the direction of the carbinol carbon. If bonds are equally distributed, attack on a *cis*-disubstituted bond proceeds more readily than a *trans* bond. Mercuric acetate ring opening is compared to that induced by acid, highly sensitive to steric hindrance.

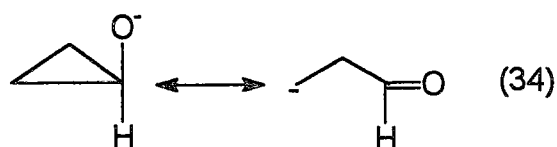
It is very interesting that although cyclopropanes in general are not reactive toward halogenating agents, cyclopropanols show a great tendency [40, 41]. In these reactions, *tert*-butyl hypohalite or N-bromosuccinimide are used instead of bromine or chlorine. Because, with bromine or chlorine the corresponding halide is a by-product of the opening and may compete with the halogen as the electrophile. Halogen openings seem to be more sensitive to electronic effects than either proton or mercuric ion openings.

#### 1.4.7.2. Reactions Induced by Bases.

Studies of the reactions of cyclopropanols in the presence of base have indicated that the ring opening occurs more readily toward the ring carbon atom which can best stabilize a negative charge [38, 41, 42] (33).



Since cyclopropanol may be regarded as the simplest homoenol, the cyclopropylalkoxide ion is one of the pair of anions which constitute the most fundamental type of homoenolate anion (34).



The ring-opening reactions of some cyclopropanols can be explained in terms of free carbanions. There are a lot of studies based on this resonance.

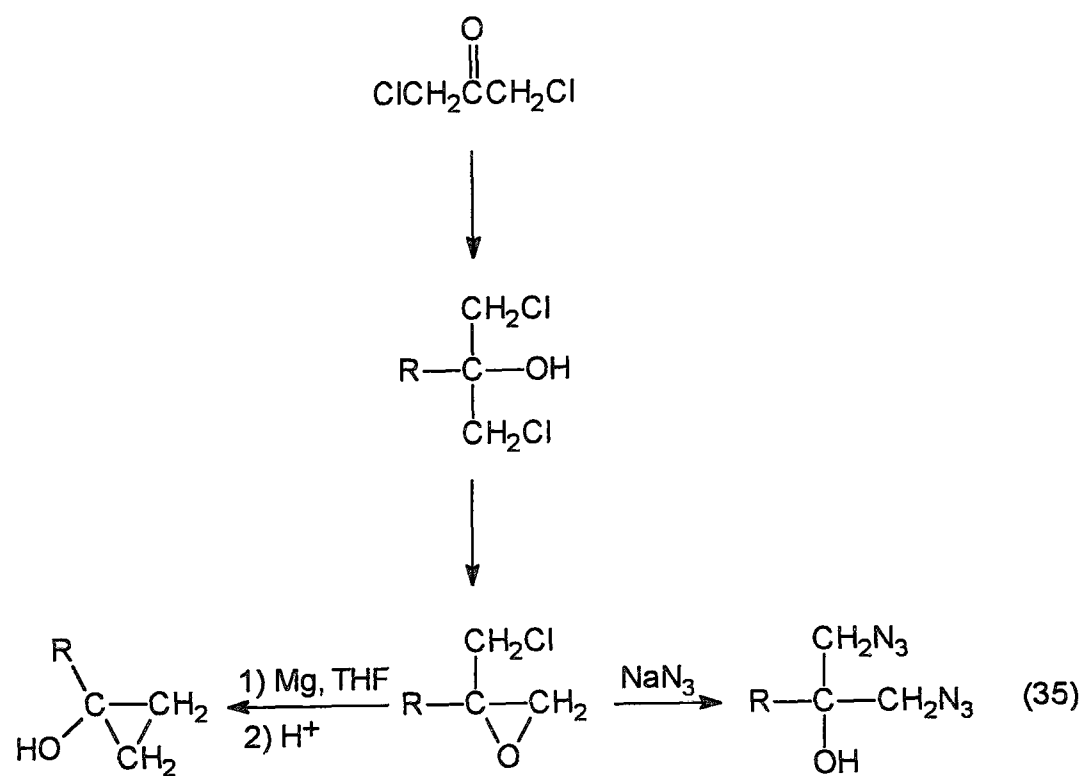
#### 1.4.7.3. Reactions Initiated by O-X Bond Cleavage.

Studies show that the O-X bond of cyclopropanols and their derivatives (X=H or NO) undergo homolytic cleavage easily. Cyclopropanols which can form stable free radicals by C<sub>1</sub>-C<sub>2</sub> bond cleavage are subject to

DePuy et. al. [44] studied the oxidations of cyclopropanols by photoexcited aryl ketones.

### 1.5. The Aim of the Work.

The aim of this work is to find an alternative way for the synthesis of 2-alkyl and 2-aryl epichlorohydrins, which are very valuable intermediates for numerous transformations, to investigate their reactions with nucleophiles, and to synthesize cyclopropanols from mentioned epichlorohydrins. We planned to synthesize 2-substituted epichlorohydrins via 2-substituted dichlorohydrins by starting from dichloroacetone. Epichlorohydrins are susceptible to the nucleophilic attack by different nucleophiles and their reactions could afford a quaternary carbon atom which could be a very useful compound for the asymmetric synthesis. By the reaction of the epichlorohydrins with sodium azide, the azido functional group will be introduced into the molecule and corresponding azido alcohols will be prepared. 1-Substituted cyclopropanols will be obtained via the intermolecular rearrangement of the Grignard reagents of the epichlorohydrins which can also cause other products (35).

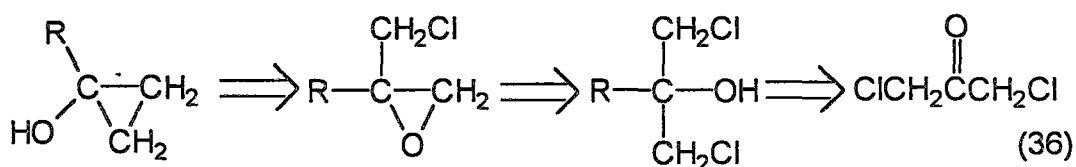


## CHAPTER II

### RESULTS AND DISCUSSION

In this work, it was planned to synthesize dichlorohydrins, 2-substituted epichlorohydrins, 1-substituted cyclopropanols, and azido alcohols.

In retro synthetic way, the Grignard reaction of 2-substituted epichlorohydrins should give 1-substituted cyclopropanols via ring-closure and ring-opening reactions. Again according to this synthetic route, it should be possible to synthesize epichlorohydrins via ring-closure reaction of dichlorohydrins. The synthesis of dichlorohydrin can be possible from Grignard reaction of dichloroacetone (36).



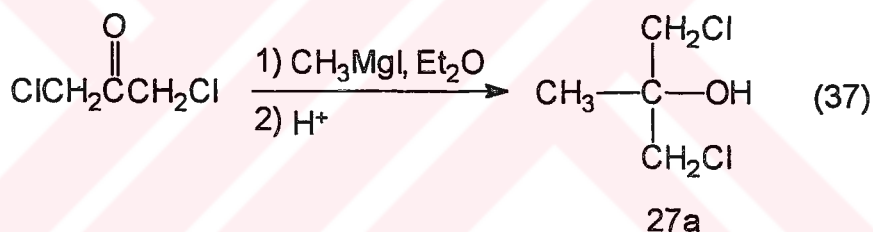
#### 2.1. The Synthesis of 2-Substituted Epichlorohydrins.



### 2.1.1. The Grignard Reaction of Dichloroacetone, The Synthesis of 1-Chloro-2-(chloromethyl)alkanols (Dichlorohydrins).

According to retro synthetic way the first part is the synthesis of dichlorohydrins.

The reaction of the Grignard reagent, which was prepared from methyl iodide and magnesium in ether, with dichloroacetone - which has the advantages of having high reactivity toward various nucleophiles, being commercially available substance, and having the possibility of synthesizing in the laboratory - gave the desired alcohol, 1-chloro-2-(chloromethyl)-2-propanol 27a in 97 % yield after hydrolysis of the reaction mixture with dilute acid and purification of the crude product (37).



The  $^1\text{H}$ -NMR spectrum of the 27a shows a singlet at 3.63 ppm for  $\text{CH}_2\text{Cl}$  protons, a broad singlet at 2.42 ppm for OH proton, and a singlet at 1.40 ppm for  $\text{CH}_3$  protons. The IR spectrum shows a broad peak for OH absorption at  $3500\text{ cm}^{-1}$  and a peak between  $2920\text{--}2980\text{ cm}^{-1}$  for C-H stretching.

The same procedure was applied for the other alkyl and aryl halides and the corresponding dichlorohydrins were isolated in very good yields (79 - 97 %) as shown in Table 1.

Table 1. Dichlorohydrins (27) from alkyl and aryl halides, RX, (26).

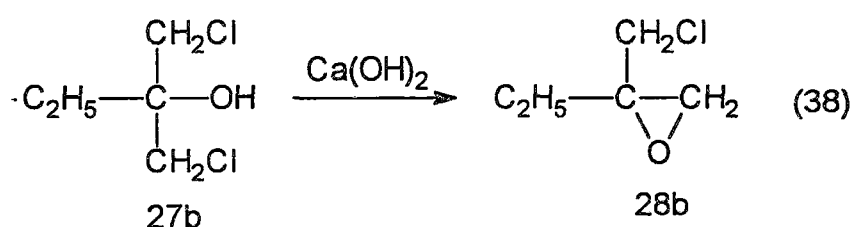
RX	Dichlorohydrins	% Yield
$\text{CH}_3\text{I}$ 26a	$\begin{array}{c} \text{CH}_2\text{Cl} \\   \\ \text{CH}_3-\text{C}-\text{OH} \\   \\ \text{CH}_2\text{Cl} \end{array}$ 27a	97
$\text{C}_2\text{H}_5\text{Br}$ 26b	$\begin{array}{c} \text{CH}_2\text{Cl} \\   \\ \text{C}_2\text{H}_5-\text{C}-\text{OH} \\   \\ \text{CH}_2\text{Cl} \end{array}$ 27b	97
$i\text{-C}_3\text{H}_7$ 26c	$\begin{array}{c} \text{CH}_2\text{Cl} \\   \\ i\text{-C}_3\text{H}_7-\text{C}-\text{OH} \\   \\ \text{CH}_2\text{Cl} \end{array}$ 27c	79
$\text{C}_4\text{H}_9\text{Cl}$ 26d	$\begin{array}{c} \text{CH}_2\text{Cl} \\   \\ \text{C}_4\text{H}_9-\text{C}-\text{OH} \\   \\ \text{CH}_2\text{Cl} \end{array}$ 27d	91
$\text{C}_6\text{H}_5\text{Br}$ 26e	$\begin{array}{c} \text{CH}_2\text{Cl} \\   \\ \text{Ph}-\text{C}-\text{OH} \\   \\ \text{CH}_2\text{Cl} \end{array}$ 27e	95

All of the isolated products were colorless oils and they were purified by column chromatography by using ethyl acetate : hexane (1:5) mixture.

The typical  $^1\text{H}$ -NMR data of the products show that  $\text{CH}_2\text{Cl}$  protons give a singlet at 3.60 ppm and protons of the aryl and alkyl groups give peaks at corresponding ppm values. IR data are also similar to the IR spectrum of 27a. Namely, we observe a broad peak for OH absorption at  $3500\text{ cm}^{-1}$  and a peak between  $2980\text{--}2900\text{ cm}^{-1}$  for the C-H stretching in the IR spectra of 27b, 27c, 27d, and 27e.

### 2.1.2. The Synthesis of 2- Substituted Epichlorohydrins.

The next step in our work involved the oxirane ring formation reaction. The transformation of dichlorohydrin 27b into 2-substituted epichlorohydrin 28b by using  $\text{Ca}(\text{OH})_2$  and water under stirring at  $55\text{ }^\circ\text{C}$  is illustrated in scheme (38). Here,  $\text{Ca}(\text{OH})_2$  works as a base and abstracts the proton of the alcohol, oxygen attacks to  $\text{CH}_2\text{Cl}$  carbon,  $\text{Cl}^-$  ion leaves the molecule and then the desired product 2-chloromethyl-2-ethyloxirane is obtained in 62 % yield after the purification.



$^1\text{H}$ -NMR spectrum of 2-chloromethyl-2-ethyloxirane shows a triplet at 0.95 ppm for  $\text{CH}_3$  protons, a quartet at 1.80 ppm for  $\text{CH}_2$  protons, a singlet at 2.75 ppm for  $\text{CH}_2\text{O}$  protons and a multiplet between 3.25-3.75 ppm for

diastereotopic  $\text{CH}_2\text{Cl}$  protons. IR spectrum shows a peak between  $3050\text{-}2990\text{ cm}^{-1}$  for the C-H stretching of the epoxy ring.

The same procedure was applied for other dichlorohydrins 27, which we obtained in the first part of the work, and the corresponding epichlorohydrins 28 were isolated in good yields (62 - 93 %) except for 2-chloromethyl-2-isopropoxyloxirane 28c (25 %) as shown in Table 2. The low yield of 28c may be due to the steric effects and experimental conditions.

The isolated products were again colorless oils and they were purified by column chromatography by using ethyl acetate : hexane (1:5).

The characteristic spectroscopic data were obtained for all products. In other words,  $^1\text{H-NMR}$  spectra show a singlet at 2.80 ppm for  $\text{CH}_2\text{O}$  protons and a multiplet between 3.40-3.80 ppm for  $\text{CH}_2\text{Cl}$  protons. IR spectra show a peak between  $3050\text{-}2990\text{ cm}^{-1}$  for the C-H stretching of the epoxy ring.

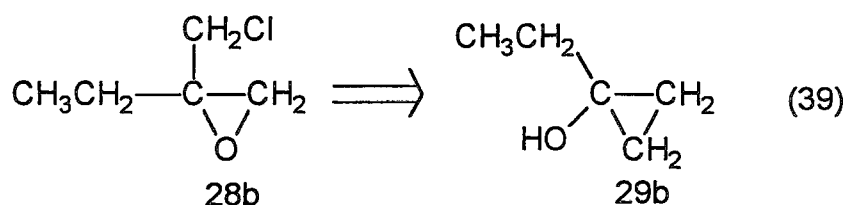
Table 2. Epichlorohydrins (28) from dichlorohydrins (27)

Dichlorohydrins	Epichlorohydrins	Reaction Time (h)	% Yield
$\begin{array}{c} \text{CH}_2\text{Cl} \\   \\ \text{CH}_3-\text{C}-\text{OH} \\   \\ \text{CH}_2\text{Cl} \end{array}$ <p>27a</p>	$\begin{array}{c} \text{CH}_2\text{Cl} \\   \\ \text{CH}_3-\text{C}-\text{CH}_2 \\   \quad \diagup \\ \text{O} \end{array}$ <p>28a</p>	7	62
$\begin{array}{c} \text{CH}_2\text{Cl} \\   \\ \text{C}_2\text{H}_5-\text{C}-\text{OH} \\   \\ \text{CH}_2\text{Cl} \end{array}$ <p>27b</p>	$\begin{array}{c} \text{CH}_2\text{Cl} \\   \\ \text{C}_2\text{H}_5-\text{C}-\text{CH}_2 \\   \quad \diagup \\ \text{O} \end{array}$ <p>28b</p>	6	62
$\begin{array}{c} \text{CH}_2\text{Cl} \\   \\ i\text{-C}_3\text{H}_7-\text{C}-\text{OH} \\   \\ \text{CH}_2\text{Cl} \end{array}$ <p>27c</p>	$\begin{array}{c} \text{CH}_2\text{Cl} \\   \\ i\text{-C}_3\text{H}_7-\text{C}-\text{CH}_2 \\   \quad \diagup \\ \text{O} \end{array}$ <p>28c</p>	8	25
$\begin{array}{c} \text{CH}_2\text{Cl} \\   \\ \text{C}_4\text{H}_9-\text{C}-\text{OH} \\   \\ \text{CH}_2\text{Cl} \end{array}$ <p>27d</p>	$\begin{array}{c} \text{CH}_2\text{Cl} \\   \\ \text{C}_4\text{H}_9-\text{C}-\text{CH}_2 \\   \quad \diagup \\ \text{O} \end{array}$ <p>28d</p>	7	63
$\begin{array}{c} \text{CH}_2\text{Cl} \\   \\ \text{Ph}-\text{C}-\text{OH} \\   \\ \text{CH}_2\text{Cl} \end{array}$ <p>27e</p>	$\begin{array}{c} \text{CH}_2\text{Cl} \\   \\ \text{Ph}-\text{C}-\text{CH}_2 \\   \quad \diagup \\ \text{O} \end{array}$ <p>28e</p>	7	68

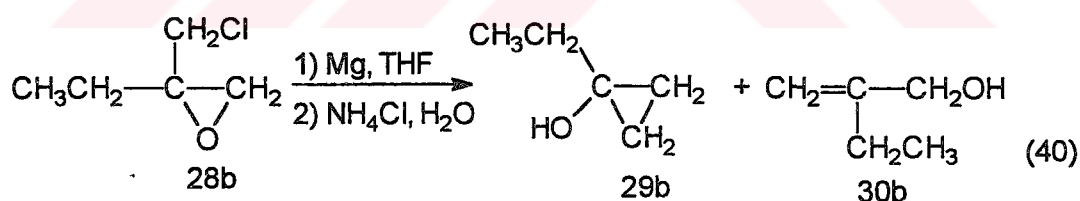
## 2.2. The Reactions of 2- Substituted Epichlorohydrins.

### 2.2.1. The Synthesis of Cyclopropanols and Allylic Alcohols.

According to retro synthetic scheme, we tried to synthesize 1-substituted cyclopropanols from the 2-substituted epichlorohydrins. The reaction of 2-chloromethyl-2-ethyloxirane 28b with Mg in THF under reflux should have given the 1-ethylcyclopropanol 29b, via the intramolecular Grignard reaction through our estimations (39).



From spectroscopic data we understood that we obtained two different products. The crude  $^1\text{H}$ -NMR and IR spectra of the product showed that not only did we get 1-ethylcyclopropanol 29b, but also we obtained 2-methylene-1-butanol (2-ethylallyl alcohol) 30b (40).

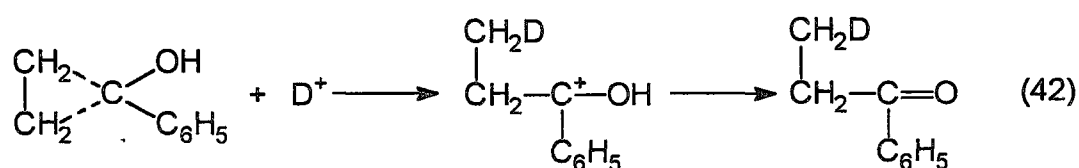


$^1\text{H}$ -NMR spectrum of crude product shows that a multiplet between 0.45-0.90 ppm for ring protons, a triplet at 0.99 ppm for  $\text{CH}_3$  protons, a quartet at 1.43 ppm for  $\text{CH}_2$  protons ( $\text{CH}_2\text{CH}_3$ ), and a singlet at 3.53 ppm for OH proton indicates the presence of 1-ethylcyclopropanol. A triplet at 0.99 ppm for  $\text{CH}_3$  protons, a quartet at 2.05 ppm for  $\text{CH}_2$  protons ( $\text{CH}_2\text{C}=\text{C}$ ), a broad singlet at 2.57



We encountered some problems during this work. We had to use acid very carefully. Because, excess use of the acid or standing for a few day caused 1-substituted cyclopropanols change into corresponding ketones [45]. It was proved by GC analysis by using standards,  $^1\text{H}$ -NMR and IR spectra.

In general, cyclopropanes open under the influence of acidic reagents so as to form the most stable carbonium ion. The resulting carbonium ion may rearrange, eliminate in one of several directions, react with solvent, or give rise to any one of a number of products. Cyclopropanols, on the other hand, and especially 1-substituted cyclopropanols, share almost none of these disadvantages. The hydroxyl group, having the ability of stabilizing an adjacent positive charge, controls and facilitates the ring opening so that one product is formed. The intermediate carbonium ion, by loss of the hydroxyl group, is converted completely to stable ketonic products. This type of conversion is known in the literature. For example, 1-phenylcyclopropanol is converted quantitatively to propiophenone. If a deuterio acid is used, a single  $\beta$ -deuterium atom is introduced into the ketone (42).



Another problem arising from our reaction is the low yield of the products. It is because of the difficulty of isolating the relatively volatile alcohols from the large amount of ether.

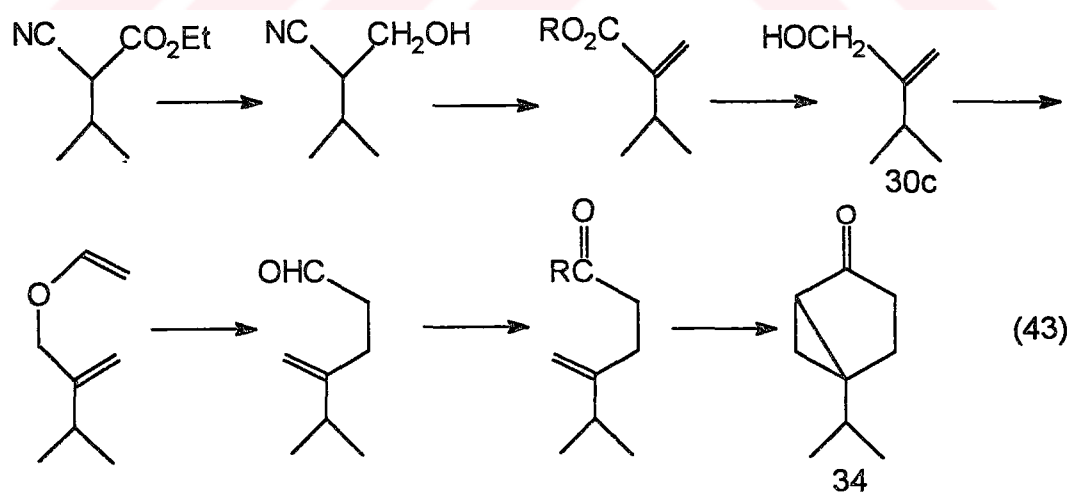


In our planning, we were expecting to synthesize only cyclopropanols. However, we obtained two different alcohols and 2-substituted allyl alcohol was the major product of the reaction.

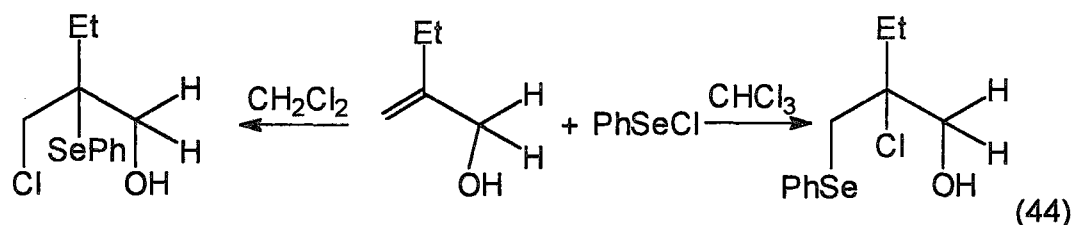
Allyl alcohols are used for numerous transformations as intermediates. They are important starting materials for asymmetric epoxidation [46]. In the Sharpless asymmetric epoxidation, they are converted to optically active epoxides in better than 90 % enantiomeric excess.

The synthesis of allylic alcohols gains importance in that they are significant intermediates for the synthesis of biologically active compounds as mentioned below.

In one study, synthesis of monoterpenes, racemic sabina ketone 34 is described via the intermediate 2-isopropylallyl alcohol 30c which is the one of the our products [47] (43).



Liotta et. al. [48] showed that terminal allylic alcohols are quite unique in their reactions with phenylselenenyl chloride. Terminal allylic alcohols react with phenylselenenyl chloride under kinetic conditions ( $-78\text{ }^{\circ}\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ ) to provide anti-Markovnikov adducts and under thermodynamic conditions ( $25\text{ }^{\circ}\text{C}$ ,  $\text{CHCl}_3$ , or  $\text{CH}_3\text{CN}$ ) to produce Markovnikov adducts (44).



We use epoxides to obtain allyl alcohols. The isomerization of epoxides to allylic alcohols is a common and preparatively useful functional group interchange. The formation of allylic alcohols from epoxides is assumed to proceed by a  $\beta$ -elimination pathway. Obviously, relief of ring strain provided sufficient driving force to overcome the reluctance of ether oxygen atoms to act as nucleofugal leaving groups in  $\beta$ -elimination reactions.

Epoxides are converted to allylic alcohols [49] by treatment of several reagents. For example, in some studies [50, 51] lithium alkylamides are used and the effect of variation of base structure has been explored.

One of the reagents used for the conversion of epoxides to allylic alcohols is *t*-butyldimethylsilyl iodide [52]. Ring opening involves cleavage of the bond to the more highly substituted carbon.

Another reagent used for the above conversion is methylmagnesium N-cyclohexylisopropylamide [53]. This reagent has some advantages over the lithium amides. Here, allyl alcohol is obtained without significant ketone or conjugate diene formation.

Mordini and coworkers [54] explored that the mixture of lithium diisopropylamide and potassium *tert*-butoxide (Lidakor reagent) promotes smooth ring opening of oxiranes to afford allyl alcohols.

Yamamoto and Nozaki [55] used a diethylaluminum dialkylamide,  $R_2NAlEt_2$ , for the preparation of allyl alcohols. The method discovered by Cope [56], and further developed by Crandall and Rickborn [57, 51], involves isomerization with lithium diethylamide.

The selenoxide reaction has been used for the synthesis of allylic alcohols by a lot of investigators [58, 59, 60, 61, 62].

As it is seen, a lot of ways are there for the synthesis of allyl alcohols. But, their synthesis are not easy. They involve more steps than ours and they have some disadvantages. For example, selenoxide is very toxic and it is not used in the production of natural and pharmacological products. Moreover, yield is low in these reactions.

Although our aim was the synthesis of cyclopropanols, we obtained two products, each of them was extremely important intermediates in synthetic organic chemistry, as a mixture. So, for this part of the our work we have to find

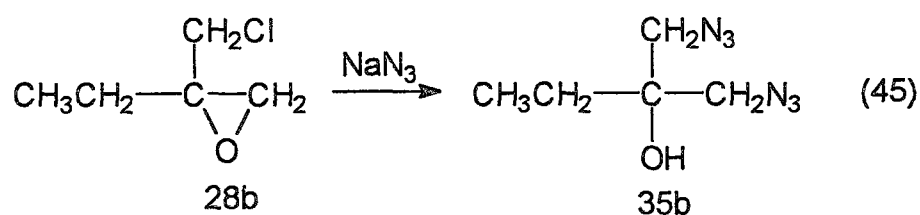
out a new method which either enables to separate the products or to convert cyclopropanol to allyl alcohol.

### 2.2.2. The Reactions of Sodium Azide With 2-Substituted Epichlorohydrins.

In this part of the our work, we tried to open oxirane ring by using  $\text{NaN}_3$  in a nucleophilic ring-opening reaction manner to obtain azido alcohols.

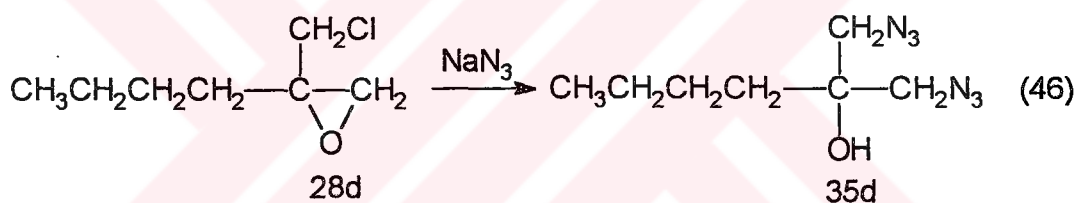
Epoxides react with  $\text{NaN}_3$  to give  $\beta$ -azido alcohols. Such reactions are very valuable due to the importance of the azido alcohols. This result arises from the fact that azido alcohols are converted easily to aziridines which are significant compounds for the synthesis of amino alcohols and amino acids. Amino alcohols are used as drugs and they are important starting materials for many drugs as well. Nucleophilic opening of aziridine ring gives many products with polyfunctional groups.

Firstly, 2-chloromethyl-2-ethyloxirane 28b was reacted with  $\text{NaN}_3$  in dioxane under reflux. After the purification of the crude product, we obtained a colorless oil which was identified by using spectroscopic methods (IR, NMR) as a diazido alcohol 35b in 89 % yield (45).



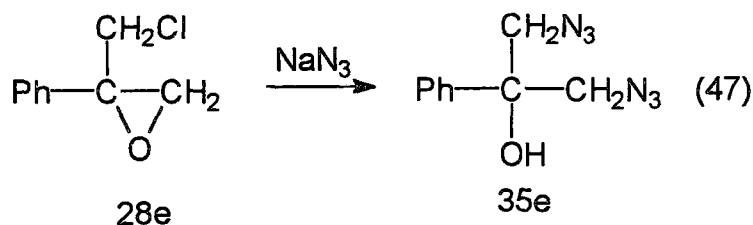
From the spectroscopic data we infer that the azide ion attacks from the less substituted carbon atom and chlorine group replaces with azide group.  $^1\text{H}$ -NMR spectrum of 35b shows a triplet at 0.93 ppm for  $\text{CH}_3$  protons, a quartet at 1.55 ppm for  $\text{CH}_2$  protons, a broad singlet at 2.08 ppm for OH proton and a singlet at 3.35 ppm for  $\text{CH}_2\text{N}_3$  protons. IR spectrum shows a strong peak at  $2050\text{ cm}^{-1}$  for azido group, a peak between  $2950\text{--}2800\text{ cm}^{-1}$  for C-H absorption and a broad peak around  $3500\text{ cm}^{-1}$  for O-H absorption. We can show that OH peak disappears by  $\text{D}_2\text{O}$  exchange by  $^1\text{H}$ -NMR spectrum.

The same reaction was carried out with 2-butyl-2-(chloromethyl)oxirane 28d as shown in scheme 46 and we obtained the corresponding diazido alcohol 35d in 74 % yield.



Spectroscopic data are in agreement with the results of the diazido alcohol 35b.  $^1\text{H}$ -NMR spectrum of 35d shows a broad singlet at 2.75 ppm for OH proton and a multiplet between 3.30-3.80 ppm for  $\text{CH}_2\text{N}_3$  protons. IR spectrum shows a strong peak at  $2100\text{ cm}^{-1}$  for azido group, a peak between  $2950\text{--}2850\text{ cm}^{-1}$  for C-H absorption and a broad peak around  $3500\text{ cm}^{-1}$  for O-H absorption.

As a next, we tried to make a reaction using 2-chloromethyl-2-phenyloxirane 28e and sodium azide to control the selectivity of the ring-opening reaction in the presence of phenyl group as a substituent (47).



Spectroscopic analysis of the product 35e shows that ring-opening reaction occurs again from the carbon atom bearing the least substituent.

$^1\text{H}$ -NMR spectrum of 35e shows a broad singlet at 3.15 ppm for OH proton, a singlet at 3.60 ppm for  $\text{CH}_2\text{N}_3$  protons and a multiplet between 7.20-7.60 ppm for aromatic protons. IR spectrum shows a sharp peak at  $2100\text{ cm}^{-1}$  for azido group, a peak between  $2850\text{-}3000\text{ cm}^{-1}$  for C-H absorption, and a broad peak around  $3500\text{ cm}^{-1}$  for O-H absorption.

By this reaction, we see that sterical effect is more effective than electronic effect.

In literature mono- substituted oxirane ring (and this substituent is phenyl) is opened from the carbon atom bearing the phenyl group. Although usual case is from the less hindered side, phenyl substituted oxirane ring-opening reactions occur at the proximal carbon atom. Because, steric hindrance is not always the only factor to influence the regioselectivity of epoxide ring-opening reactions. In addition to steric effects, electronic effects can play an important role in these reactions. Electronically, a substituent may exert its effect through resonance or induction or both. Resonance donating substituents, such as phenyl, promote ring-opening at the proximal carbon atom [12].

Our regioselective ring-opening reaction of oxirane with phenyl substituent gave product according to our alkyl substituted oxirane ring reactions, i.e., from the less hindered side of the ring. This regioselectivity can be explained by the sterical hindrance of the carbon atom with phenyl group. Because, we do not have a secondary carbon atom with phenyl substituent but instead we have a quaternary carbon atom. This can give extra hindrance for nucleophilic attack. That's why our oxirane opened from less hindered side. We could not find examples for ring-opening reactions with quaternary carbon atoms. Such an example does not exist in the literature.



## CHAPTER III

### EXPERIMENTAL

Nuclear magnetic resonance ( $^1\text{H}$ ) spectra were recorded on a Bruker AC 80 MHz FT-NMR spectrometer. Chemical shifts are reported in parts per million ( $\delta$ ) downfield from an internal tetramethylsilane reference. Spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Infrared spectra were recorded on a Nicolet 510 FT-IR spectrometer. Band positions are reported in reciprocal centimeters ( $\text{cm}^{-1}$ ). 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 effected 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.

All other commercially available reagents and reactants were obtained in reagent grade. Diethyl ether was distilled from sodium-benzophenone ketyl.



### 3.1. The Synthesis of 1-Chloro-2-(chloromethyl)-2-propanol (27a).

To the solution of Mg turnings (1.7 g, 71.0 mmol) in diethyl ether (30.0 ml) in a 200 ml round-bottomed flask equipped with a dropping funnel and reflux condenser consisting of calcium chloride tube was added dropwise a solution of methyl iodide (10.3 g, 73.0 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. This 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 hydrochloric acid (5.0 ml), respectively. The resulting mixture was extracted with diethyl ether (3 x 25 ml). The combined organic layer was washed with brine and dried over MgSO<sub>4</sub>. Final purification by flash column chromatography using 5:1 *n*-hexane/ethyl acetate as the eluent yielded 1-chloro-2-(chloromethyl)-2-propanol (9.1 g, 97 %).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ(ppm) 1.40 (s, 3H, CH<sub>3</sub>)

2.42 (broad s, 1H, OH)

3.63 (s, 4H, CH<sub>2</sub>Cl)

IR (neat) : 3500, 2980-2920 cm<sup>-1</sup>

### 3.2. The Synthesis of 1-Chloro-2-(chloromethyl)-2-butanol (27b).

The procedure described for the preparation of 27a was repeated using ethyl bromide (2.7 g, 25.0 mmol), magnesium turnings (0.6 g, 25.0 mmol) and dichloroacetone (3.2 g, 25.0 mmol) to afford 3.8 g (97 %) of 1-chloro-2-(chloromethyl)-2-butanol.

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  0.95 (t,  $J=7$  Hz, 3H,  $\text{CH}_3$ )  
1.65 (q,  $J=7$  Hz, 2H,  $\text{CH}_2$ )  
2.30 (broad s, 1H, OH)  
3.40-3.70 (m, 4H,  $\text{CH}_2\text{Cl}$ )

IR (neat) : 3500, 2980-2920  $\text{cm}^{-1}$

### 3.3. The Synthesis of 1-Chloro-2-(chloromethyl)-3-methyl-2-butanol (27c).

The procedure described for the preparation of 27a was repeated using isopropyl chloride (5.9 g, 75.0 mmol), magnesium turnings (1.8 g, 75.0 mmol) and dichloroacetone (9.5 g, 75.0 mmol) to afford 10.1 g (79 %) of 1-chloro-2-(chloromethyl)-3-methyl-2-butanol.

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  1.05 (d,  $J=7$  Hz, 6H,  $\text{CH}_3$ )  
1.60-1.80 (m, 1H, CH)  
2.30 (broad s, 1H, OH) ( $\text{D}_2\text{O}$  exchange)  
3.60-3.80 (m, 4H,  $\text{CH}_2\text{Cl}$ )

IR (neat) : 3500, 2900-2980  $\text{cm}^{-1}$

### 3.4. The Synthesis of 1-Chloro-2-(chloromethyl)-2-hexanol (27d).

The procedure described for the preparation of 27a was repeated using butyl chloride (2.3 g, 25.0 mmol), magnesium turnings (0.6 g, 25.0 mmol) and dichloroacetone (3.2 g, 25.0 mmol) to afford 4.2 g (91 %) of 1-chloro-2-(chloromethyl)-2-hexanol.

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  0.95 (t,  $J=7$  Hz, 3H,  $\text{CH}_3$ )  
1.50-1.90 (m, 6H,  $\text{CH}_2$ )  
2.25 (broad s, 1H, OH)  
3.50-3.62 (m, 4H,  $\text{CH}_2\text{Cl}$ )

IR (neat) : 3500, 2980-2900  $\text{cm}^{-1}$

### 3.5. The Synthesis of 1,3-Dichloro-2-phenyl-2-propanol (27e).

The procedure described for the preparation of 27a was repeated using bromobenzene (8.0 g, 50.0 mmol), magnesium turnings (1.2 g, 50.0 mmol) and dichloroacetone (6.0 g, 50.0 mmol) to afford 10.0 g (95 %) of 1,3-dichloro-2-phenyl-2-propanol.

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  3.03 (s, 1H, OH)  
4.05-4.15 (m, 4H,  $\text{CH}_2\text{Cl}$ )  
7.30-7.60 (m, Ar-H)

IR (neat) : 3500, 2980-3030  $\text{cm}^{-1}$

### 3.6. The Synthesis of 2-Chloromethyl-2-methyloxirane (28a).

To the solution of calcium hydroxide (1.9 g, 26.2 mmol) in water (13.4 ml) in a 100 ml round-bottomed flask equipped with a reflux condenser 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<sub>4</sub>. Final purification was achieved by flash column chromatography using 5:1 *n*-hexane/ethyl acetate as the eluent to yield 2-chloromethyl-2-methyloxirane (2.3 g, 62 %).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ(ppm) 1.20 (s, 3H, CH<sub>3</sub>)  
2.80 (s, 2H, CH<sub>2</sub>O)  
3.45-3.55 (m, 2H, CH<sub>2</sub>Cl)  
IR (neat) : 3050- 2990 cm<sup>-1</sup>

### 3.7. The Synthesis of 2-Chloromethyl-2-ethyloxirane (28b).

The procedure described for the preparation of 28a was repeated using 1-chloro-2-(chloromethyl)-2-butanol (3.0 g, 18.8 mmol), calcium hydroxide (1.0 g, 14.0 mmol) and water (6 ml) to afford 2.3 g (62 %) of 2-chloromethyl-2-methyloxirane.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ(ppm) 0.95 (t, J=7 Hz, 3H, CH<sub>3</sub>)

1.80 (q, J=7 Hz, 2H, CH<sub>2</sub>)

2.75 (s, 2H, CH<sub>2</sub>O)

3.25-3.75 (m, 2H, CH<sub>2</sub>Cl)

IR (neat) : 3050- 2990 cm<sup>-1</sup>

### 3.8. The Synthesis of 2-Chloromethyl-2-isopropylloxirane (28c).

The procedure described for the preparation of 28a was repeated using 1-chloro-2-(chloromethyl)-3-methyl-2-butanol (10.1 g, 59.0 mmol), calcium hydroxide (3.3 g, 45.0 mmol) and water (18.7 ml) to afford 1.8 g (25 %) of 2-chloromethyl-2-isopropylloxirane.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ(ppm) 0.91-1.50 (m, 6H, CH<sub>3</sub>)

1.63-1.95 (m, 1H, CH)

2.75 (s, 2H, CH<sub>2</sub>O)

3.55-3.75 (m, 2H, CH<sub>2</sub>Cl)

IR (neat) : 3050-2990 cm<sup>-1</sup>

### 3.9. The Synthesis of 2-Butyl-2-(chloromethyl)oxirane (28d).

The procedure described for the preparation of 28a was repeated using 1-chloro-2-(chloromethyl)-2-hexanol (5.4 g, 29.0 mmol), calcium hydroxide (1.6

g, 22.0 mmol) and water (9.2 ml) to afford 2.7 g (63 %) of 2-butyl-2-(chloromethyl)oxirane.

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  0.97 (t,  $J=7$  Hz, 3H,  $\text{CH}_3$ )

1.65-2.00 (m, 6H,  $\text{CH}_2$ )

2.75 (s, 2H,  $\text{CH}_2\text{O}$ )

3.55-3.80 (m, 2H,  $\text{CH}_2\text{Cl}$ )

IR (neat) : 3050-2990  $\text{cm}^{-1}$

### 3.10. The Synthesis of 2-Chloromethyl-2-phenyloxirane (28e).

The procedure described for the preparation of 28a was repeated using 1,3-dichloro-2-phenyl-2-propanol (3.3 g, 16.0 mmol), calcium hydroxide (1.8 g, 24.0 mmol) and water (10.2 ml) to afford 1.8 g (68 %) of 2-chloromethyl-2-phenyloxirane.

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  2.70-3.20 (m, 2H,  $\text{CH}_2\text{O}$ )

3.60-4.10 (m, 2H,  $\text{CH}_2\text{Cl}$ )

7.10-7.50 (m, Ar-H)

IR (neat) : 3050-2990  $\text{cm}^{-1}$

### 3.11. The Synthesis of 1-Methylcyclopropanol and 2-Methyl-2-propen-1-ol (methallyl alcohol) (29a and 30a).

The solution of magnesium turnings (0.6 g, 26.0 mmol) in dry THF (30 ml) was placed in an oven-dried, 100 ml two-necked, round-bottomed flask provided with a reflux condensor consisting of calcium chloride tube, and heated to 60 °C under stirring. 2-Chloromethyl-2-methyloxirane (2.3 g, 21.0 mmol) in dry THF (10 ml) was added dropwise. The solution was refluxed for seven hours at 70-80 °C. Then, the reaction mixture was washed with cold saturated ammonium chloride solution (20 ml) and followed by 1 N hydrochloric acid (5 ml). This solution was extracted with ether (3 x 25 ml). The combined organic extract was washed with brine and dried over anhydrous  $\text{MgSO}_4$ . Evaporation of the solvent afforded 1.0 g (32.2 %) of mixture.

For 1-methylcyclopropanol (29a):

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  0.40-0.70 (m, ring  $\text{CH}_2$ )

1.32 (s,  $\text{CH}_3$ )

3.50 (s, OH)

For 2-methyl-2-propen-1-ol (30a):

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  1.60 (s,  $\text{CH}_3$ )

3.60-3.85 (m,  $\text{CH}_2\text{O}$ )

4.05 (s, OH)

4.90 (d,  $J=11$  Hz,  $\text{CH}_2=\text{C}$ )

IR (neat) : 3420, 2980-2880  $\text{cm}^{-1}$

3.12. The Synthesis of 1-Ethylcyclopropanol and 2-Methylene-1-butanol (2-ethylallyl alcohol) (29b and 30b).

The procedure described for the preparation of 29a and 30a was repeated using 2-ethyl-2-(chloromethyl)oxirane (0.5 g, 4.1 mmol) and magnesium turnings (0.1 g, 5.0 mmol) to afford 0.3 g (48 %) of mixture.

For 1-ethylcyclopropanol (29b):

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  0.45-0.90 (m, ring  $\text{CH}_2$ )

0.99 (t,  $J=8$  Hz,  $\text{CH}_3$ )

1.43 (q,  $J=8$  Hz,  $\text{CH}_2$ )

3.53 (s, OH)

For 2-methylene-1-butanol (30b):

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  0.99 (t,  $J=8$  Hz,  $\text{CH}_3$ )

2.05 (q,  $J=8$  Hz,  $\text{CH}_2\text{-C}=\text{C}$ )

2.57 (broad s, OH)

4.04 (s,  $\text{CH}_2\text{O}$ )

4.90 (d,  $J=11$  Hz,  $\text{CH}_2=\text{C}$ )

IR (neat) : 3500, 2980-2880  $\text{cm}^{-1}$

3.13. The Synthesis of 1-Isopropylcyclopropanol and 2-Methylene-3-methyl-1-butanol (2-isopropylallyl alcohol) (29c and 30c).

The procedure described for the preparation of 29a and 30a was repeated using 2-chloromethyl-2-isopropoxyloxirane (1.8 g, 13.4 mmol) and magnesium turnings (0.4 g, 16.0 mmol) to afford 0.2 g (33 %) of mixture.

For 1-isopropylcyclopropanol (29c):



$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  0.30-0.60 (m, ring  $\text{CH}_2$ )  
0.95 (d,  $J=7$  Hz,  $\text{CH}_3$ )  
1.15-1.35 (m, CH)  
2.16 (s, OH)

For 2-methylene-3-methyl-1-butanol (30c):

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  1.03 (d,  $J=7$  Hz,  $\text{CH}_3$ )  
1.60-1.95 (m, CH)  
2.35 (broad s, OH)  
3.44 (s,  $\text{CH}_2\text{O}$ )  
3.69 (d,  $J=11$  Hz,  $\text{CH}_2=\text{C}$ )

IR (neat) : 3450, 2980-2880  $\text{cm}^{-1}$

3.14. The Synthesis of 1-Butylcyclopropanol and 2-Methylene-1-hexanol (29d and 30d).

The procedure described for the preparation of 29a and 30a was repeated using 2-butyl-2-(chloromethyl)oxirane (0.5 g, 3.4 mmol) and magnesium turnings (0.1 g, 4.0 mmol) to afford 0.5 g (76 %) of mixture.

For 1-butylcyclopropanol (29d):

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  0.20-0.80 (m, ring  $\text{CH}_2$ )  
0.90 (t,  $J=7$  Hz  $\text{CH}_3$ )  
1.10-1.80 (m,  $\text{CH}_2$ )  
3.15 (broad s, OH)

For 2-methylene-1-hexanol (30d):

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  0.90 (t,  $\text{CH}_3$ )  
1.10-1.80 (m,  $\text{CH}_2$ )  
2.20-2.50 (m,  $\text{CH}_2\text{-C}=\text{C}$ )  
3.75 (s, OH)  
4.05 (s,  $\text{CH}_2\text{O}$ )  
5.87 (d,  $J=11$  Hz,  $\text{CH}_2=\text{C}$ )

IR (neat) : 3450, 2960-2850  $\text{cm}^{-1}$

### 3.15. The Synthesis of 1-Phenylcyclopropanol and 2-Phenylprop-2-en-1-ol (29e and 30e).

The procedure described for the preparation of 29a and 30a was repeated using 2-chloromethyl-2-phenyloxirane (1.0 g, 5.9 mmol) and magnesium turnings (0.1 g, 5.9 mmol) to afford 0.4 g (63 %) of mixture.

For 1-phenylcyclopropanol (29e):

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  0.85-1.55 (m, ring  $\text{CH}_2$ )  
1.93 (broad s, OH)  
7.10-7.40 (m, Ar-H)

For 2-phenylprop-2-en-1-ol (30e):

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  1.60 (s, OH)  
4.50 (s,  $\text{CH}_2\text{O}$ )  
5.40 (d,  $J=11$  Hz,  $\text{CH}_2=\text{C}$ )  
7.10-7.40 (m, Ar-H)

IR (neat) : 3400, 3080-2980  $\text{cm}^{-1}$

### 3.16. The Synthesis of 1-Azido-2-(azidomethyl)-2-butanol (35b).

To the solution of 2-chloromethyl-2-ethyloxirane (0.5 g, 3.7 mmol) in dioxane (20 ml) in a 100 ml two-necked, round-bottomed flask provided with a reflux condensor was added dropwise a solution of sodium azide ( $\text{NaN}_3$ , 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  $\text{MgSO}_4$ . Evaporation of the solvent afforded 0.5 g (89 %) of 1-azido-2-(azidomethyl)-2-butanol.

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  0.93 (t,  $J=7$  Hz, 3H,  $\text{CH}_3$ )  
1.55 (q,  $J=7$  Hz, 2H,  $\text{CH}_2$ )  
2.08 (broad s, 1H, OH)  
3.35 (s, 4H,  $\text{CH}_2\text{N}_3$ )

IR(neat) : 3500, 2950-2800, 2050  $\text{cm}^{-1}$

### 3.17. The Synthesis of 1-Azido-2-(azidomethyl)-2-hexanol (35d).

The procedure described for the preparation of 35b was repeated using 2-butyl-2-(chloromethyl)oxirane (0.7 g, 4.7 mmol), sodium azide (0.8 g, 12.3

mmol) and water (2.0 ml) to afford 0.7 g (74 %) of 1-azido-2-(azidomethyl)-2-hexanol.

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  0.90 (t,  $J=7$  Hz, 3H,  $\text{CH}_3$ )  
1.10-1.80 (m, 6H,  $\text{CH}_2$ )  
2.75 (s, 1H, OH)  
3.30-3.80 (m, 4H,  $\text{CH}_2\text{N}_3$ )

IR(neat) :3500, 2950-2850, 2100  $\text{cm}^{-1}$

### 3.18. The Synthesis of 1,3-Bis(azido)-2-phenyl-2-propanol (35e).

The procedure described for the preparation of 35b was repeated using 2-chloromethyl-2-phenyloxirane (0.7 g, 4.2 mmol), sodium azide (0.7 g, 10.8 mmol) and water (2.0 ml) to afford 0.9 g (94 %) of 1,3-bis(azido)-2-phenyl-2-propanol

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta(\text{ppm})$  3.15 (broad s, 1H, OH)  
3.60 (s, 4H,  $\text{CH}_2\text{N}_3$ )  
7.20-7.60 (m, Ar-H)

IR(neat) :3500, 3000-2850, 2100  $\text{cm}^{-1}$

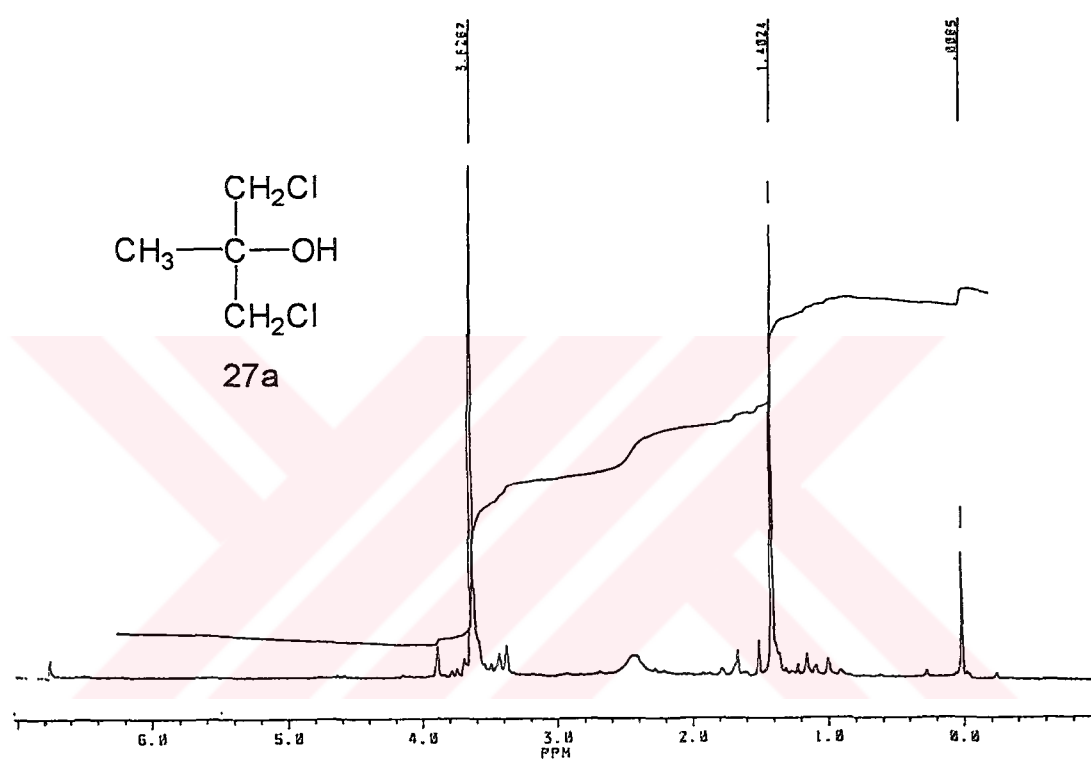


Figure 1. The  $^1\text{H}$ -NMR Spectrum of 1-Chloro-2-(chloromethyl)-2-propanol (27a)

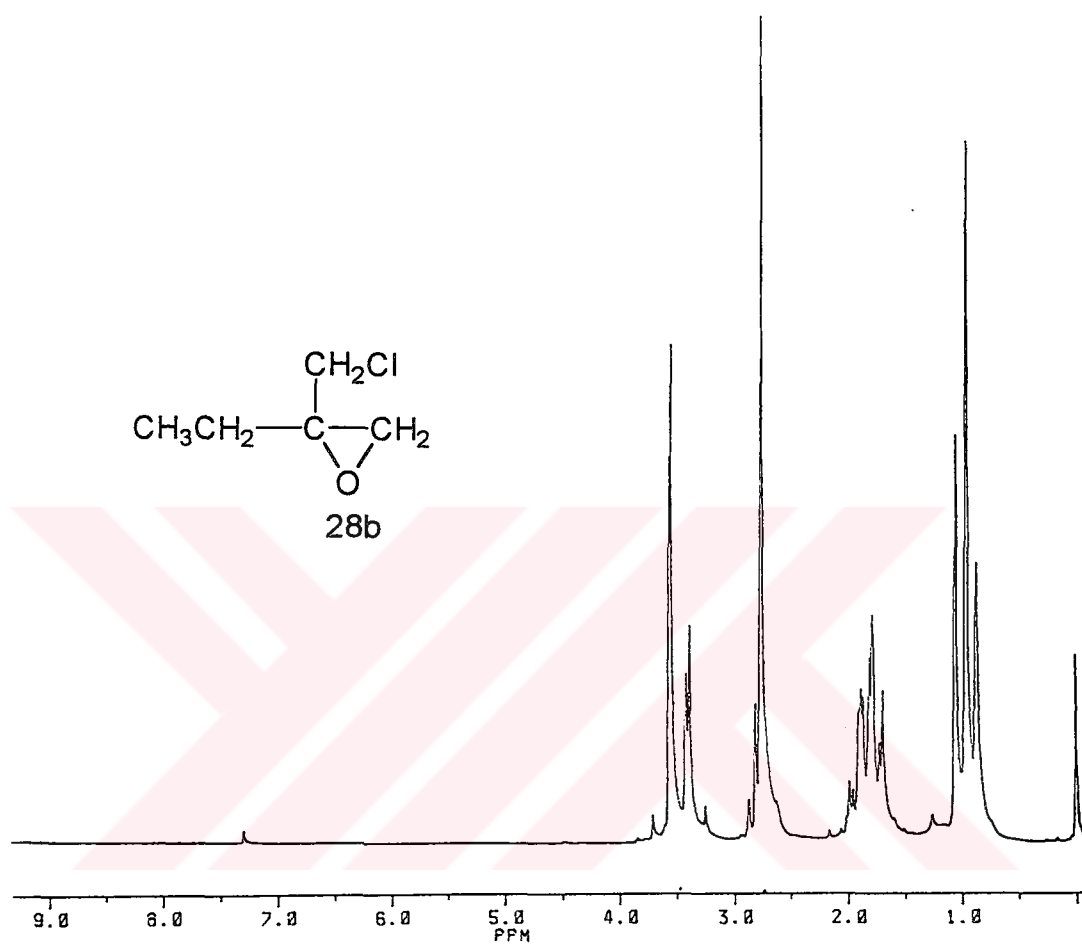


Figure 2. The <sup>1</sup>H-NMR Spectrum of 2-Chloromethyl-2-ethyloxirane (28b)

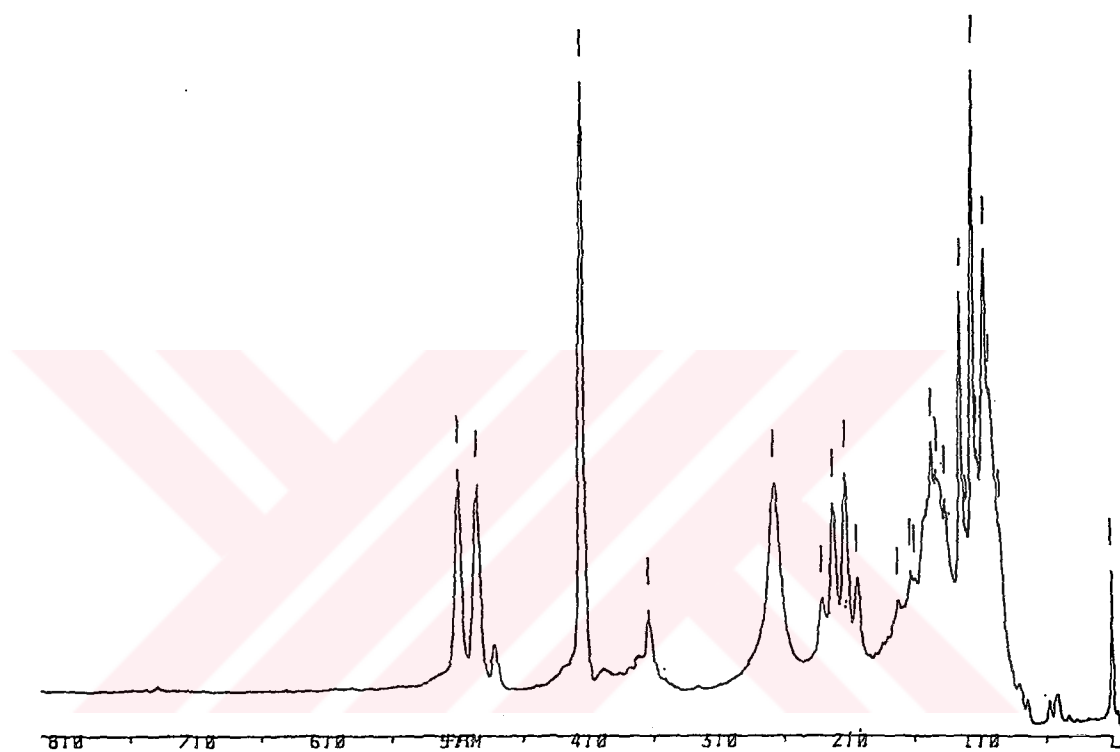
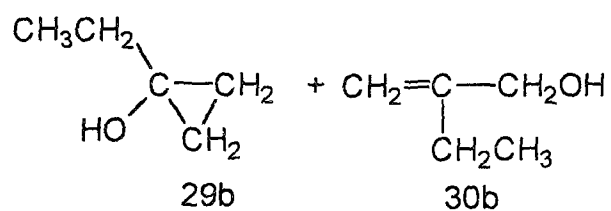


Figure 3. The  $^1\text{H}$ -NMR Spectrum of 1-Ethylcyclopropanol and 2-Methylene-1-butanol (2-ethylallyl alcohol) (29b and 30b)

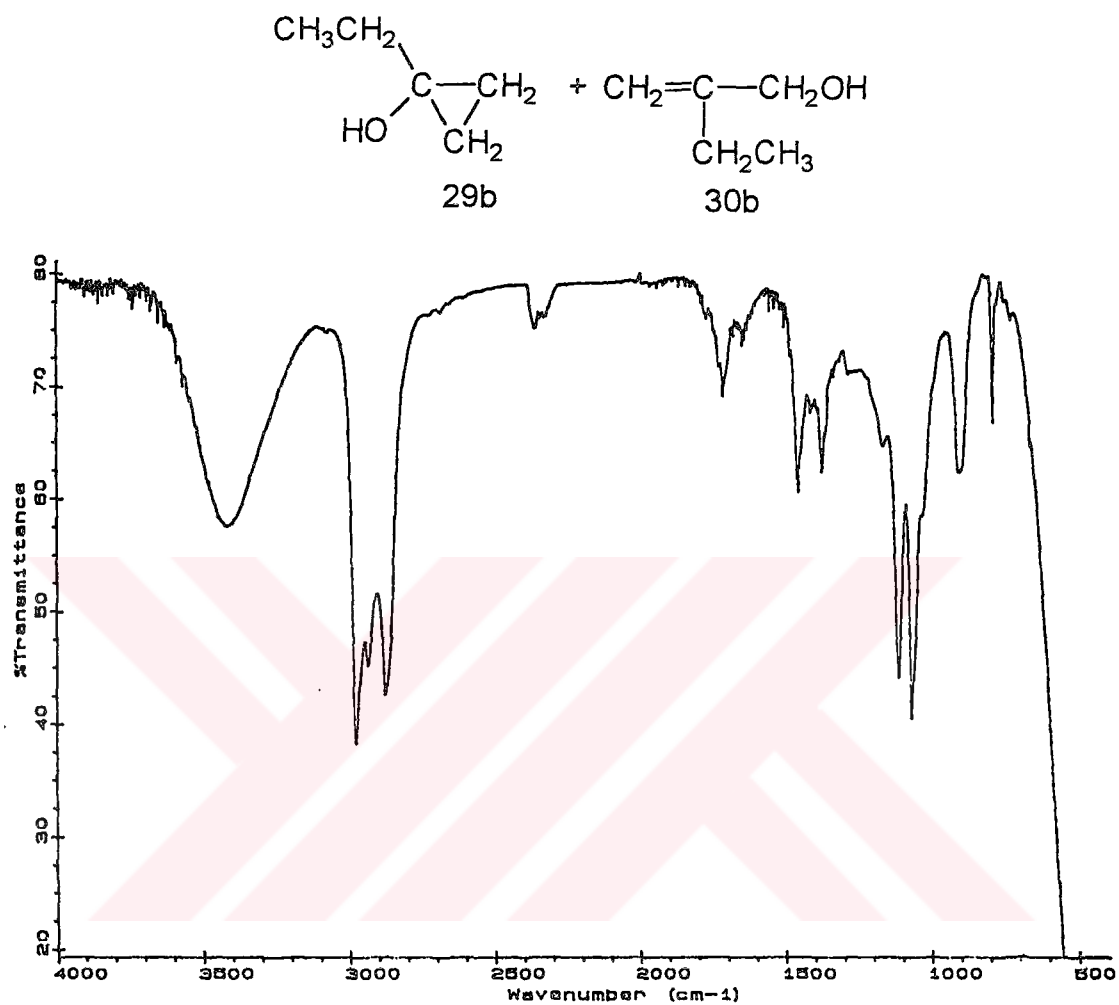


Figure 4. The IR Spectrum of 1-Ethylcyclopropanol and 2-Methylene-1-butanol (2-ethylallyl alcohol) (29b and 30b)



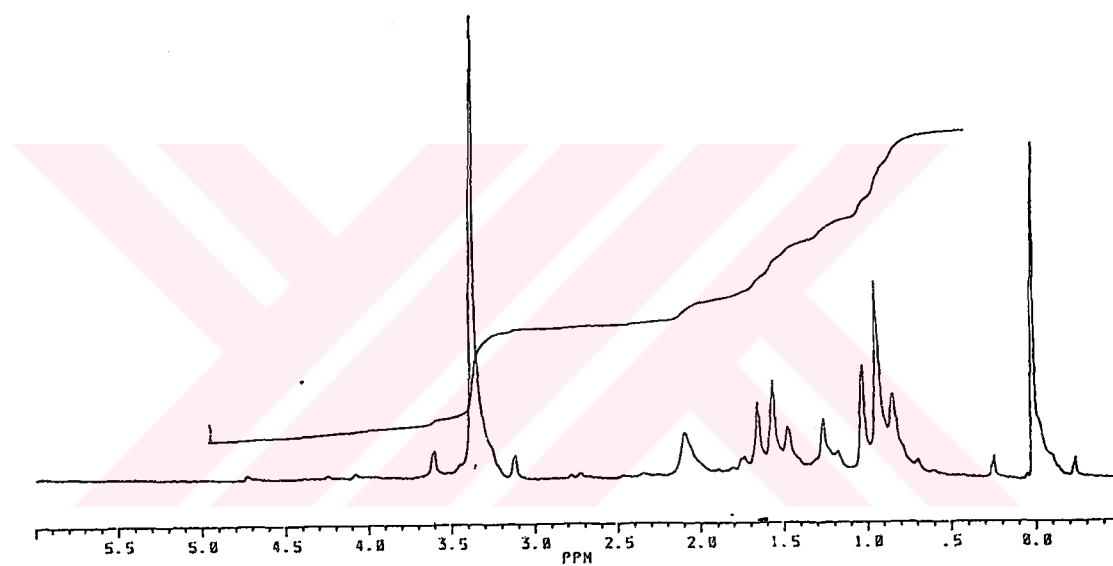
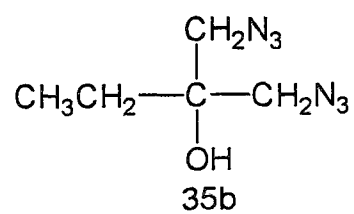


Figure 5. The  $^1\text{H}$ -NMR Spectrum of 1-Azido-2-(azidomethyl)-2-butanol (35b)

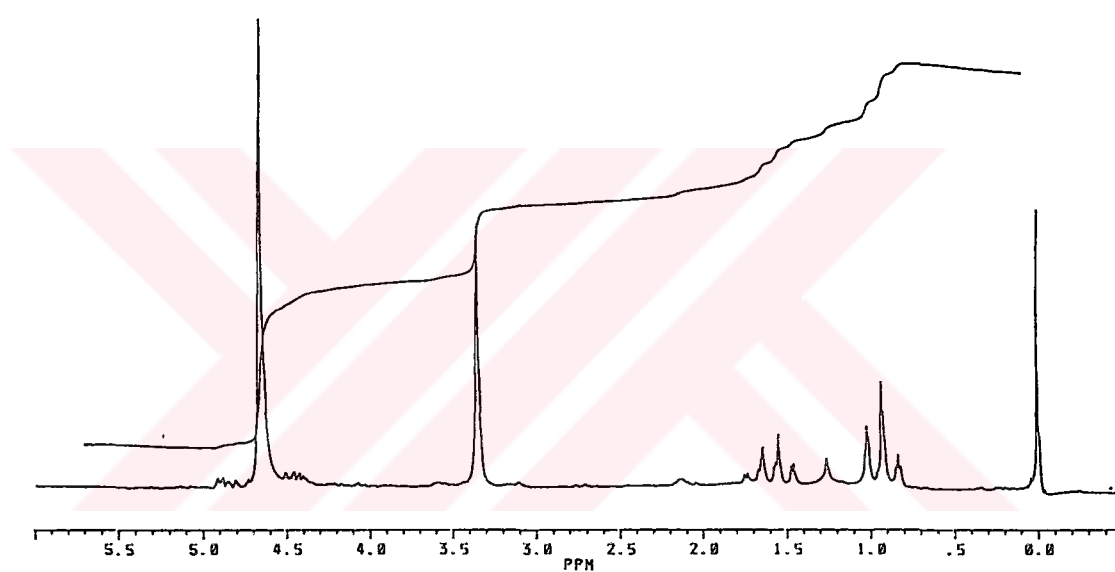
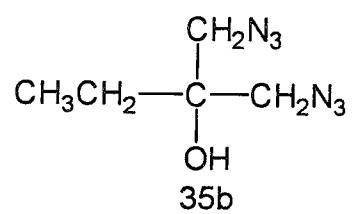


Figure 6. The  $^1\text{H}$ -NMR Spectrum of 1-Azido-2-(azidomethyl)-2-butanol (35b) with  $\text{D}_2\text{O}$

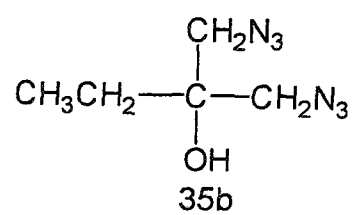


Figure 7. The IR Spectrum of 1-Azido-2-(azidomethyl)-2-butanol (35b)

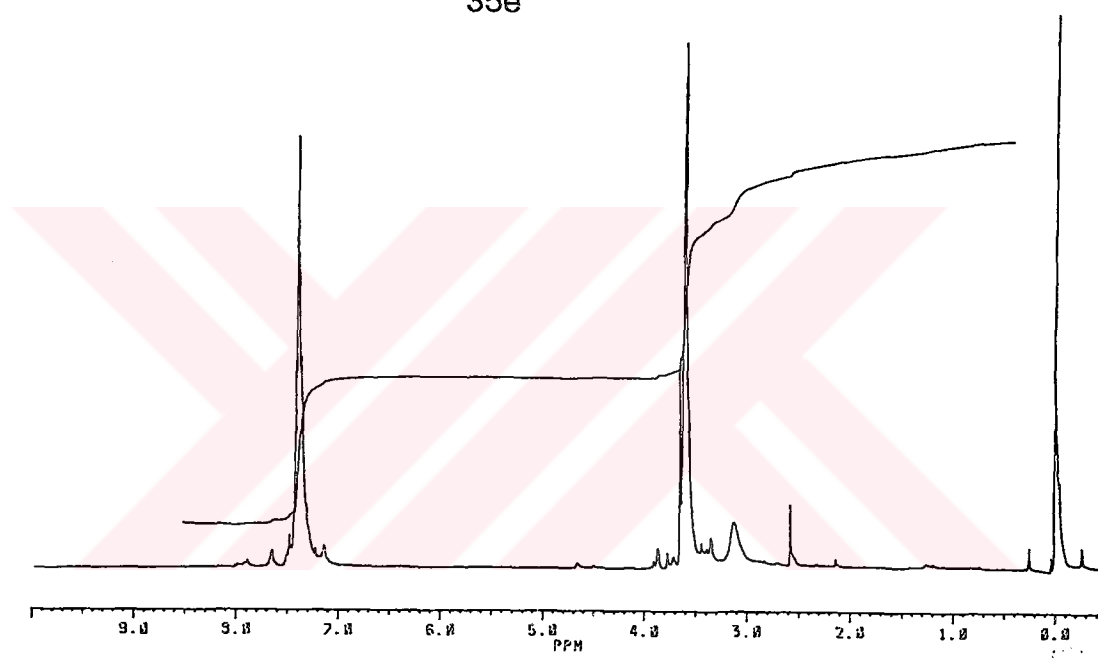
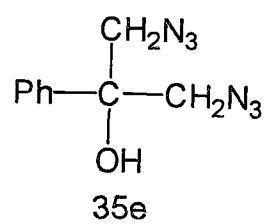


Figure 8. The  $^1\text{H}$ -NMR Spectrum of 1,3-Bis(azido)-2-phenyl-2-propanol (35e)

## CHAPTER IV

### CONCLUSION

In this study, methyl iodide, ethyl bromide, isopropyl chloride, butyl chloride, bromobenzene, and dichloroacetone were used as starting materials to synthesize 2-substituted epichlorohydrins, 1-substituted cyclopropanols, and diazido alcohols. During the course of the reaction, corresponding dichlorohydrins were synthesized and isolated. All products were characterized by  $^1\text{H}$ -NMR and IR spectroscopy.

1-Substituted cyclopropanols and 2-substituted allyl alcohols were obtained via the intramolecular rearrangement of the Grignard reagents of the 2-substituted epichlorohydrins as a mixture although expected product was 1-substituted cyclopropanols.

Diazido alcohols were obtained by the reaction of the sodium azide with 2-substituted epichlorohydrins via nucleophilic ring-opening reaction of the oxiranes. It was investigated how the presence of different substituents effects the opening of the ring. Alkyl substituted and phenyl substituted oxiranes are given ring-opening reaction from less hindered side of the ring. This is the first study done up to now for the ring-opening reaction of oxirane with a quaternary center.

It is shown that by ring-opening reaction of oxirane the more important factor is sterical hindrance than electronic effect.

In short, all of the products are of the synthetic use. They can be used for further transformations easily.



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