การแปลงอิพอกไซด์เป็นแฮโลไฮดรินและอะมิโนแอลกอฮอล์ด้วยโลหะแฮไลด์

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TRANSFORMATION OF EPOXIDES INTO HALOHYDRINS AND AMINOALCOHOLS BY METAL HALIDES

Miss Sirinuch Pattarativanont

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Petrochemistry and Polymer Science
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By	Miss Sirinuch Pattarativanont
Field of Study	Petrochemistry and Polymer Science
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ศิรินุช ภัทรทิวานนท์: การแปลงอิพอกไซด์เป็นแฮโลไฮดรินและอะมิโนแอลกอฮอล์ด้วยโลหะแฮไลด์ (TRANSFORMATION OF EPOXIDES INTO HALOHYDRINS AND AMINOALCOHOLS BY METAL HALIDES) อ. ที่ปรึกษา: ผศ. ดร.วรินทร ชวศิริ, 87 หน้า.

งานวิจัยนี้มุ่งเน้นที่จะพัฒนาวิธีการที่มีประสิทธิภาพ สำหรับปฏิกิริยาการเปิดวงแบบเลือกจำเพาะของอิพอกไซด์ที่มีหมู่แทนที่ให้เกิดขึ้นภายใต้ภาวะที่ไม่รุนแรงและรวดเร็ว โดยใช้โครเมียม(III) คลอไรด์ หรือโครเมียม(III)ไนเทรต การเปิดวงอิพอกไซด์ที่มีหมู่อัลคิลและแอริลเป็นหมู่แทนที่ด้วยโครเมียมรีเอเจนท์เหล่านี้ ให้ผลิตภัณฑ์เป็นแฮโลไฮดรินและอะมิโนแอลกอฮอล์ในปริมาณสูงถึงดีเยี่ยม กลไกแบบเลือกจำเพาะที่เกิดขึ้น จะเกิดผ่านการแตกพันธะคาร์บอนกับออกซิเจนของอิพอกไซด์ โดยมีกรดลิวอิสเป็นตัวส่งเสริม ซึ่งส่วนใหญ่จะขึ้นกับโครงสร้างตั้งต้นของอิพอกไซด์ให้ผลิตภัณฑ์เป็นแฮโลไฮดรินและอะมิโนแอลกอฮอล์ผ่านการแทนที่แบบ S_N2 วิธีการนี้สามารถเตรียมได้ง่ายภายใต้ภาวะไม่รุนแรง รวดเร็ว รีเอเจนต์หาซื้อได้ง่าย ราคาไม่แพง ไม่ว่องไวต่ออากาศ และมีความเลือกจำเพาะต่อผลิตภัณฑ์สูงเมื่อเทียบกับตัวเร่งกรดลิวอิสอื่น

สาขาวิชา ปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์ ลายมือชื่อนิสิต ศิรินุช ภัทรทิวานนท์

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#4872483123 : PETROCHEMISTRY AND POLYMER SCIENCE
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SIRINUCH PATTARATIVANONT: TRANSFORMATION OF EPOXIDES INTO HALOHYDRINS AND AMINOALCOHOLS BY METAL HALIDES. THESIS ADVISOR: ASST. PROF. WARINTHORN CHAVASIRI, Ph.D., 87 pp.

This work focuses on the development of an efficient procedure for the selective ring opening of substituted epoxides under mild and rapid conditions utilized either chromium(III) chloride or chromium(III) nitrate. The ring opening of alkyl- and aryl-substituted epoxides with these chromium(III) reagents produced halohydrin and aminoalcohol in high to excellent yield. Regioselectivity for a C-O bond cleavage of epoxide *via* Lewis acid promoted was greatly depended on the substitution pattern of epoxides furnished halohydrins and aminoalcohols through a predominantly S_N2-type mechanism. This procedure is very simple, mild, rapid, commercially available, inexpensive, insensitive to air and high selectivity of product compared to those catalyzed by other Lewis acids.

Field of study Petrochemistry and Polymer Science Student's signature S. Pattarativanont
Academic year.....2007..... Advisor's signature W. Chavasiri

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LIST OF ABBREVIATIONS

br	=	broad (NMR)
br s	=	broad singlet (NMR)
ºC	=	degree Celsius
$CDCl_3$	=	deuterated chloroform
CH_2Cl_2	=	dichloromethane
$CHCl_3$	=	chloroform
CH_3CN	=	acetonitrile
^{13}C NMR	=	carbon-13 nuclear magnetic resonance
d	=	doublet (NMR)
dd	=	doublet of doublet (NMR)
ddd	=	doublet of doublet of doublet (NMR)
dt	=	doublet of triplet
EtOAc	=	ethyl acetate
g	=	gram (s)
h	=	hour
^{1}H NMR	=	proton nuclear magnetic resonance
HMBC	=	heteronuclear multiple bond correlation experiment
HMQC	=	heteronuclear multiple quantum coherence experiment
Hz	=	hertz (NMR)
J	=	coupling constant
m	=	multiplet (NMR)
MeOH	=	methanol
min	=	minute (s)
mL	=	milliliter (s)
mmol	=	millimole (s)
m/z	=	mass to charge ratio
M^+	=	molecular ion
MS	=	mass spectrometry
MW	=	molecular weight
NMR	=	nuclear magnetic resonance

ppm	=	part per million
q	=	quartet (NMR)
quin	=	quintet (NMR)
s	=	singlet (NMR)
t	=	triplet (NMR)
td	=	triplet of doublet (NMR)
TLC	=	thin layer chromatography
δ	=	unit of chemical shift
wt	=	weight
α	=	alpha
β	=	beta
%	=	percent

CHAPTER I

INTRODUCTION

The petrochemical industry becomes more important manufacture because it provides well over 95% by tonnage of all organic chemicals. Petrochemical industry grew rapidly in the 1950s and 1960s [1]. The major change for the petrochemical industry due to increases in raw material costs, research to improve process efficiency and environmental and legislative pressures [2]. Petroleum is a mixture of hydrocarbons of different basic structures with various molecular weights. Many reactions have been reported to convert these abundant compounds to the desired products. Hydrocarbon derivatives containing oxygen or other heteroatoms are important intermediates in organic synthesis and in petrochemical industry.

The oxidation of unfunctionalized as well as functionalized olefins is still one of current interest and intensive researches in organic synthesis [3,4]. The epoxidation of alkenes is a fundamental reaction in laboratory and in chemical industry. The main reason stems from the fact that epoxides are widely utilized as intermediates in laboratory and chemical manufacturing and served as important building blocks for a variety of chemical compounds [5]. Therefore the development of efficient and selective methods for the preparation of epoxides is always called for. Epoxides can be easily prepared and due to their ring strain and high reactivity, their reactions with various nucleophiles lead to highly regio- and stereoselective ring opened products. The obtained products from epoxide are widely used in industry for manufacturing various types of products, ranging from perfumery to polymeric materials. Halohydrin and amino alcohol are important classes in organic syntheses that have considerable in the synthesis of halogenated marine natural products and can be utilized for some useful synthetic transformation. One of the most straightforward synthetic approaches for the preparation of these halohydrins and amino alcohols involves in the ring opening reactions of epoxides [6].

1.1 Literature review on the transformation of epoxides into halohydrins and amino alcohols

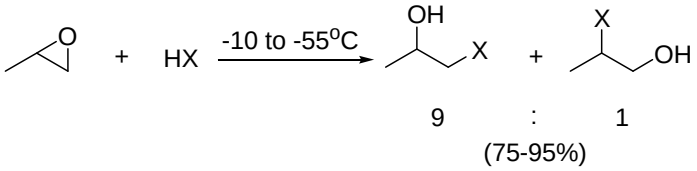
Epoxides are widely used as raw materials such as epoxy resins, paints, surfactants, and are very essential key intermediates in many important organic transformation reactions. The synthetically useful reactions of epoxide are indeed important in organic synthesis, pharmaceutical industries, perfumery and other chemical fields. Because of epoxides ring strain they prone to react with a large number of various substants. For example, ring opening of epoxides with heteroatom nucleophiles [7], with carbon nucleophiles [8], intramolecular ring opening [9], reduction to alcohols [10], deoxygenation to olefins [11], rearrangement to allylic alcohols [12], or to carbonyl compounds [13], *etc*. Among those epoxide-related transformations, the ring opening of epoxides into halohydrins and amino alcohols is a well-investigated reaction. Because of the variety advantages of these products, it was attended to study in this transformation.

1.1.1 The transformation of epoxides into halohydrins

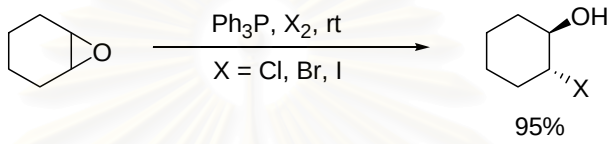
Among ring opening products from epoxides, halohydrins are one of important classes. The advantages of halohydrin are widely ranged in organic synthesis, for example, *vic*-halohydrins have considerable importance in the synthesis of halogenated marine natural products and were utilized for some useful synthetic transformations [14]. In addition, halohydrins are versatile intermediates in the synthesis of a vast range of biologically active natural and synthetic products, unnatural amino acids and chiral auxiliaries for asymmetric synthesis [15]. Moreover, they are also utilized in the synthesis of β-adrenegic blockers and are key intermediates in the preparation of homochiral β-blockers [16].

Typically, the most common method for the synthesis of 1,2-halohydrins from epoxides is their ring opening either with hydrogen halides or with hydrohalogenic acids [17]. However, the searching for new and efficient methodologies has still been the relevant topic of current interest.

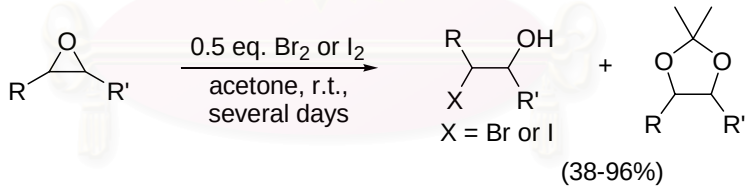
According to the literature review, in 1953 Stewart and VanderWerf reported the ring opening of propylene oxide by HCl, HBr and HI. The extent of attack on the secondary carbon by halide ion had been found to increase in the order of Cl > Br > I. The reaction products were a mixture of two isomers in 75-95 % yield [18].



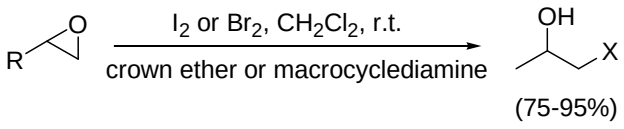
In 1983 Palumbo and coworkers addressed one pot treatment of epoxides with triphenylphosphine and a proper halogen under mild conditions at room temperature. The quantitative yield of chloro-, bromo- and iodo- hydrins was obtained [19].

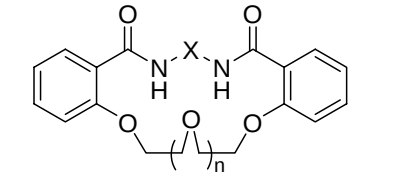


In 1992 Konaklieva *et al.* published the work on the bromination and iodination reactions of epoxide. Alkyl, aryl and disubstitued epoxides were allowed to react with elemental bromine and iodine in various solvents. The dramatic rate acceleration is observed for reaction in acetone, but the formation of by-products was obtained. The reactions required only 0.5 molar equivalents of iodine or bromine to complete the reaction with by-products such as acetate detected [20].

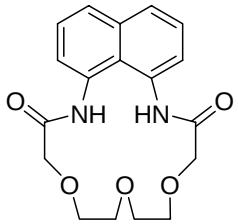


In 1998 Sharghi and colleagues reported the novel macrocyclic diamides (**A**, **B**) and crown ethers (**C**, **D**, **E**) used as catalysts in the highly regioselective halogenative cleavage of epoxides with elemental halogen (I_2 and Br_2). The reaction was preformed under mild reaction conditions in various aprotic solvents. The halohydrins can be synthesized in high yield.

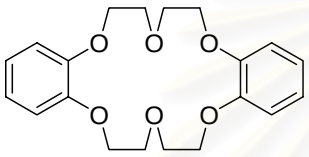




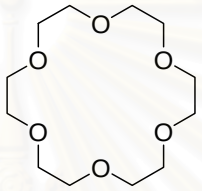
(**A**)



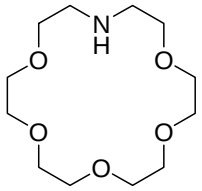
(**B**)



dibenzo-18-crown-6 (**C**)



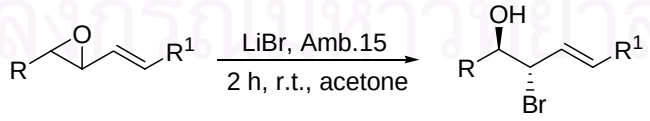
18-crown-6 (**D**)



aza-18-crown-6 (**E**)

The major advantages of this method are high regioselectivity, simple regeneration of catalyst and its reuse through several cycles without a decrease in activity and ease of workup of the reaction [21].

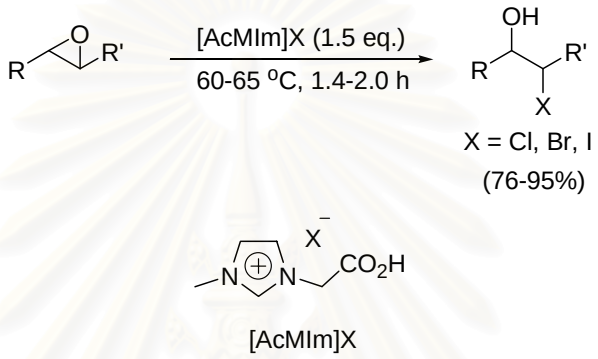
Moreover, in 2000 Antonioletti and coworkers reported the ring opening of vinyl epoxides by LiBr/Amb 15. The regio- and stereoselectivity of the epoxide ring opening with LiBr/Amb 15 did not depend on the size of R. The yield of the reaction was very high for R′= CO_2Et and quite good for R′= alkyl. The known high reactivity of the allylic position could be responsible for the complete regioselectivity observed, particularly when an electron withdrawing constituent on the double bond makes this position more electron deficient.



The advantage of this study was the importance of the products obtained, due to the possibility of substituting the halide, and to functionalize further the double

bond. The employment of this methodology in the synthesis of polyhydroxylated chains, subunits present in many naturally occurring compounds [22].

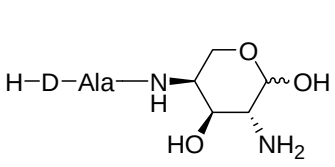
In 2005 Ranu and Banerjee reported the use of ionic liquid, [AcMIm]X to diverse aliphatic or cyclic epoxides to produce the corresponding halohydrins in high yield without any catalyst and solvent. The cleavages are considerably fast reaction (1-2 h) and highly regio- and stereoselective. The reaction was going through an S_N2 addition path under mild conditions [23].



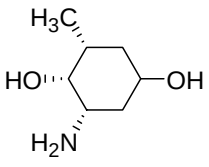
1.1.2 The transformation of epoxides into aminoalcohols

1,2-Amino alcohols are key intermediates to many organic compounds, mainly in biologically active natural and synthetic products [24] and are chiral auxilliaries for asymmetric synthesis. In addition, 1,2-aminoalcohols are also important molecules in medicinal chemistry [25].

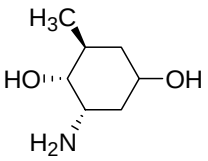
1,2-Aminoalcohols are wildly used in pharmaceutically application [26]. For examples: Prumycin (**F**) is an antifungal antibiotic and has an interesting antitumor activity. L-Daunosamine (**G**) is the carbohydrate component of a group of important anticancer anthracyclin antibiotics such as adriamycin, daunomycin and carminomycin. D-Ristosamine (**H**), the enantiomer of carbohydrate component of the antibiotic ristomycin. L-Vancosamine (**I**) was isolated as a carbohydrate component of the antibiotics vancomycin and sporaviridin.



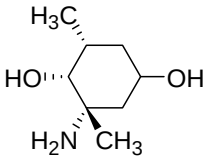
Prumycin (**F**)



L-Daunosamine (**G**)

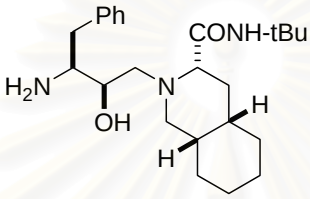


D-Ristosamine (**H**)

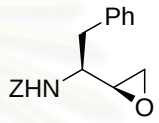


L-Vancosamine (**I**)

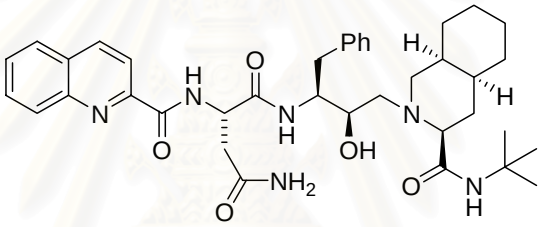
Aminoalcohol (**J**) obtained from the epoxide (**K**) is an important intermediate for a synthesis of an important HIV-protease inhibitor, Saquinavir (**L**).



(**J**)

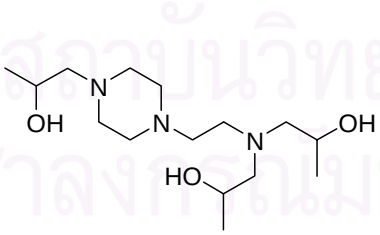


(**K**)

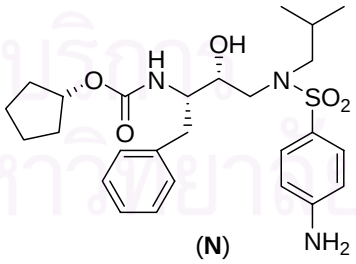


(**L**)

Recently, the aminoalcohol (**M**) has been reported to selectively interact with RNA. This molecule as a mixture of diastereomers was discovered during a random screening of commercially available aminoalcohols as an anti HIV agent. Another important aminoalcohol derivative is amprenavir (**N**), a second generation HIV protease inhibitor with a number of clinical advantages.



(**M**)

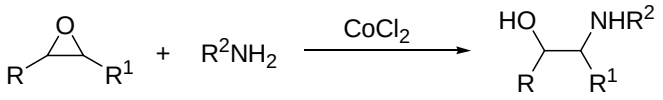


(**N**)

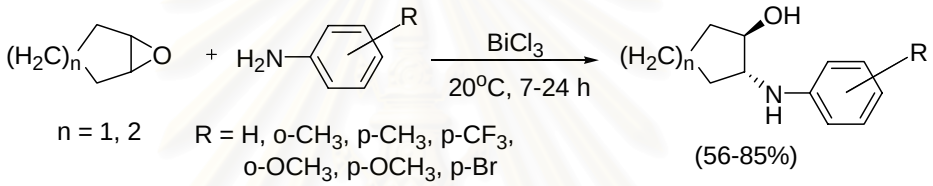
Aminoalcohols can generally be prepared using a variety of routes, most commonly through the ring opening of epoxides [27].

In 1990 Iqbal and Pandey reported the utilization of $CoCl_2$ in the regioselective cleavage of oxiranes with aniline and *p*-methylaniline to the

corresponding β-aminoalcohols in excellent yields (60-78%). Benzylic and aliphatic amines, however, do not react under these conditions [28].

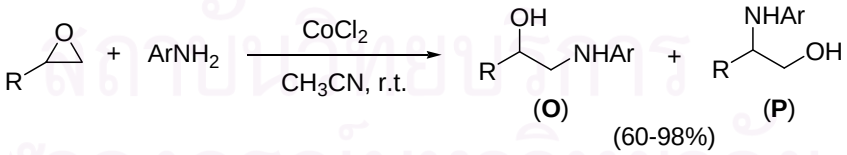


In 2002 Ollevier and Lavie-Compin addressed a novel, mild and efficient method for the nucleophilic opening of epoxides with aromatic amines in the presence of catalytic amount of $BiCl_3$. Cyclohexene oxide and cyclopentene oxide were used as models reacting with various amines.



This method was compatible with deactivated and sterically hindered aromatic amines. Products were obtained in 56-85 % yield [29].

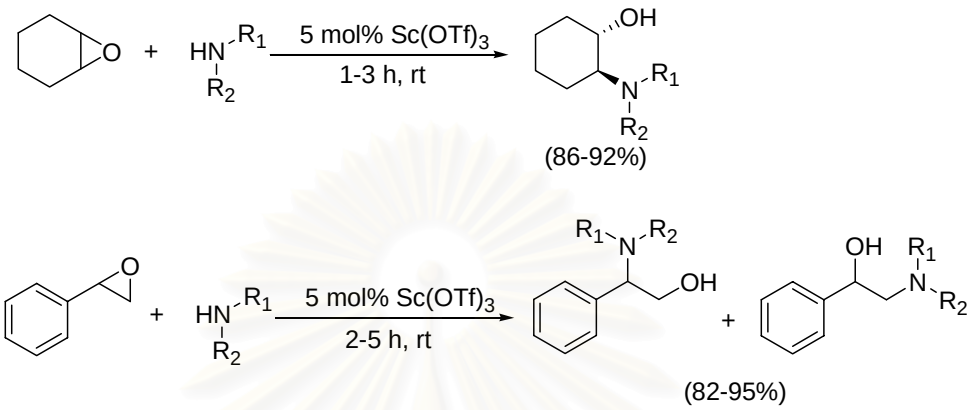
In 2004 Sundararajan and coworkers used $CoCl_2$ as a mild and efficient catalyst for regioselective ring opening of oxiranes with aniline yielding β-aminoalcohols in good yields. Styrene oxides underwent regioselective addition of anilines at the highly substituted carbon to yield regioisomer **P**, predominantly.



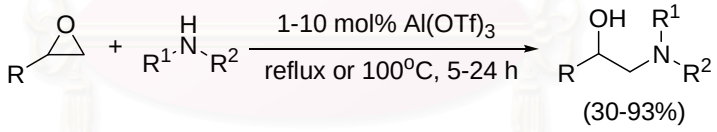
In strict contrast, the aliphatic oxirane gave a major product with the opposite regiochemistry. Benzylamine and other aliphatic amines failed to the ring opening of oxirane even after long reaction periods with only trace amount of the expected product aminoalcohols being observed [30].

In 2005, Placzek and coworkers reported the simple and efficient method for the synthesis of β-aminoalcohols by ring opening of oxiranes in the presence of a

catalytic amount of $Sc(OTf)_3$ at room temperature under solvent free conditions. The reaction works well with both aromatic and aliphatic amines. High regio- and diastereoselectivity can be considered as a noteworthy advantage of this method [31].



Recently, in 2006, Williams and Lawton reported the use of $Al(OTf)_3$ as an efficient Lewis acid catalyst for the ring opening of epoxides. This catalyst was found to be highly active, producing the desired amino alcohol products in high yields with low catalyst loadings. A range of epoxides including cyclohexene oxide, 1-butene oxide, *t*-butyl glycidyl ether and 1-butenyl glycidyl ether could be ring opened by various alkyl- and arylamines [32].



Epoxides are powerful starting materials for a range of useful materials and can be converted into, amongst others, halohydrins and aminoalcohols. The development of more efficient catalyst for conversion of epoxides to halohydrins and amino alcohols has been a significant goal for organic synthesis and industrial point of view. The search for cheap, simple and selective protocol often focuses on metal halide. An interesting example is $CrCl_3.6H_2O$ and $Cr(NO_3)_3.9H_2O$ for transformation of epoxides in short period of time under mild conditions. These chromium salts and complexes are commercially available and inexpensive. The several advantages such as high catalytic activities and reactivities, stable in air and moisture and simplify in the experimental was made these reagents applicable to the reaction. In addition, there

was no report on the utilization of these chromium reagents for catalytic ring opening of epoxide into halohydrins and aminoalcohols. Catalytic efficiency of these complexes was screened using the transformation of cyclohexene oxide as a model substrate. After the reaction was optimized, it will then apply to a variety of different epoxides.

1.2 The goal of this research

The aims of this research can be summarized as follows.

1. To study the optimum conditions for the transformation of epoxides into halohydrins and aminoalcohol using $CrCl_3.6H_2O$ and $Cr(NO_3)_3.9H_2O$.
2. To apply the optimum conditions for the transformation of selected epoxides into halohydrins.
3. To apply the optimum conditions for the transformation of selected amines and epoxides to aminoalcohols.

CHAPTER II

EXPERIMENTAL

2.1 General procedure

The weight of all chemical substances was determined on a Precisa electrical balance XT220A. The injection volume of chemicals was used by micropipette Biohit for 1-100 and 100-1000 μL scale. Evaporation of solvents was carried out on a Bücchi Rotavapor R-114 equipped with a water aspirator Eyela model A-3S. The magnetic stirrers were from Corning. Chromatography: thin layer chromatography (TLC) performed on Merck D.C. Kieselgel 60 F_{254} 0.2 mm precoated aluminium plates cat. No. 1.05554 and visualized using UV light at 254 nm or dipping into aq $KMnO_4$ reagent. Column chromatography was performed on silica gel (Merck's, Kieselgel 60 G) and aluminium oxide 90 (70-230 mesh ASTM). Gas chromatographic analysis was carried out on a Variance GC-3800 chromatograph instrument equipped with flame ionization detector (FID) with nitrogen as a carrier gas. The column used was a capillary column type of CP-wax (30 m x 0.25 mm).

The ^{1}H- and ^{13}C-NMR spectra were performed in deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as an internal reference on Varian nuclear magnetic resonance spectrometer, model Mercury plus 400 NMR spectrometer which operated at 399.84 MHz for ^{1}H and 100.54 MHz for ^{13}C nuclei. The chemical shifts (δ) are assigned by comparison with residue solvent protons. The FIDs were processed and integrated after a base-line correction using Mestrec23 software from Mestrelab Research.

2.2 Chemical reagents

All chemicals were purchased from Fluka, Merck or Aldrich, and were used as received without any further purification except aniline, benzylamine and *N*-methylaniline which were distilled under ambient pressure. Commercial grade

solvents were distilled before use in column chromatography. Solvents for reactions were reagent grade and used without purification.

2.3 Synthesis of authentic sample

***trans*-2-Chlorocyclohexanol synthesis**

Cyclohexene oxide 0.101 mL (1 mmol) was added to a solution of $CrCl_3.6H_2O$ (1 mmol) in THF (5 mL) in a round bottom flask with magnetic bar. The reaction was refluxed with continuous stirring for 1 h. The reaction was allowed to cool down to room temperature. The mixture was extracted with Et_2O and H_2O. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum.

trans-2-Chlorocyclohexanol (**2**): colorless oil, ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.66-3.72 (1H, td, *J* = 4.2, 10.1 Hz), 3.47-3.50 (1H, td, *J* = 4.3, 9.1 Hz), 2.74 (1H, br s), 2.17-2.20 (1H, m), 2.05-2.07 (1H, m), 1.56-1.81 (3H, m) and 1.15-1.39 (3H, m).

***trans*-2-(Phenylamino)cyclohexanol**

Cyclohexene oxide 0.101 mL (1 mmol) was added to a solution of $Cr(NO_3)_3.9H_2O$ (0.1 mmol) and aniline (5 mmol) in THF (5 mL) in a round bottom flask. The mixture was then reflux for 30 min with continuous stirring. After the reaction was completed, the reaction mixture was taken and diluted with Et_2O and then washed with distilled water 2 times. The organic layer was dried over anhydrous Na_2SO_4 then evaporated in vacuum to obtain product.

trans-2-(Phenylamino)cyclohexanol (**23**): yellow solid, ^{1}H-NMR ($CDCl_3$), δ (ppm) : 7.16-7.20 (2H, t, *J* = 7.8 Hz), 6.71-6.77 (3H, dd, *J* = 7.6, 15.5 Hz), 3.33-3.38 (1H, td, *J* = 4.2, 9.7 Hz), 3.12-3.18 (1H, ddd, *J* = 3.9, 9.2, 10.9 Hz), 2.40 (1H, br s), 2.11-2.14 (2H, m), 1.71-1.79 (2H, m), 1.29-1.42 (3H, m) and 1.00-1.11 (1H, m).

***trans*-2-Bromo- and *trans*-2-iodocyclohexanol**

To a solution of chromium catalyst (0.3 mmol) and additive, such as LiBr or LiI, in THF (5 mL) was added cyclohexene oxide 0.101 mL (1 mmol). The mixture was then stirred at reflux temperature for 5 min. After the reaction was completed, the reaction mixture was taken and diluted with Et_2O and then washed with distilled water 2 times. The organic layer was dried over anhydrous Na_2SO_4 and removed solvent by evaporated in vacuum.

trans-2-Bromocyclohexanol (**3**): light yellow oil, ^{1}H-NMR ($CDCl_3$), δ (ppm): 3.85-3.91 (1H, ddd, *J* = 4.2, 9.4, 11.8 Hz), 3.55-3.61 (1H, td, *J* = 4.5, 9.8 Hz), 2.66

(1H, s), 2.29-2.35 (1H, m), 2.09-2.12 (1H, m), 1.65-1.87 (3H, m) and 1.20-1.40 (3H, m).

trans-2-Iodocyclohexanol (**4**): brown oil, ^{1}H-NMR ($CDCl_3$), δ (ppm): 4.00-4.08 (1H, td, *J* = 4.1, 10.9 Hz), 3.63-3.67 (1H, td, *J* = 4.3, 9.9 Hz), 2.45-2.56 (1H, m), 2.23-2.36 (1H, m), 1.71-2.13 (3H, m) and 1.20-1.53 (3H, m).

***trans*-2-Nitroxycyclohexan-1-ol and *trans*-4-(2-nitrooxycyclohexyloxy)-butan-1-ol**

Cyclohexene oxide 0.101 mL (1 mmol) was added to a solution of $Cr(NO_3)_3.9H_2O$ (1 mmol) in THF (5 mL) in a round bottom flask with magnetic bar. The reaction was refluxed with continuous stirring for 1 h. The reaction was allowed to cool down to room temperature. The mixture was extracted with Et_2O and H_2O. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was a mixture of two compound, *trans*-2-nitroxycyclohexan-1-ol and *trans*-4-(2-Nitrooxy-cyclohexyloxy)-butan-1-ol, separated by silica gel column using 4:1 hexane:EtOAc as an eluent.

trans-2-Nitroxycyclohexan-1-ol (**5**): colerless oil, ^{1}H-NMR ($CDCl_3$), δ (ppm): 4.77-4.83 (1H, td, *J* = 4.6, 9.7 Hz), 3.61-3.67 (1H, td, *J* = 4.8, 9.9 Hz), 2.04-2.18 (3H, m), 1.74-1.77 (2H, m) and 1.23-1.48 (3H, m).

trans-4-(2-Nitrooxy-cyclohexyloxy)-butan-1-ol (**6**): colerless oil, ^{1}H-NMR ($CDCl_3$), δ (ppm): 4.46-4.49 (2H, t, *J* = 6.5 Hz), 3.62-3.67 (1H, dt, *J* = 6.3, 9.3 Hz), 3.37-3.43 (2H, dt, *J* = 5.9, 9.3 Hz), 2.98-3.04 (1H, ddd, *J* = 4.2, 8.8, 10.4 Hz), 2.62 (1H, br s), 1.98-2.00 (1H, m), 2.04-2.07 (1H, m) 1.78-1.85 (2H, m), 1.65-1.72 (4H, m) and 1.05-1.32 (4H, m).

Alkoxyalcohol, *trans*-2-methoxycyclohexan-1-ol

To a solution of $Cr(NO_3)_3.9H_2O$ (0.3 mmol) in MeOH (10 mL) was added cyclohexene oxide 0.101 mL (1 mmol). The mixture was then stirred at reflux temperature for 1 h. After the reaction was completed, the reaction mixture was taken and extracted with Et_2O and then washed with distilled water 2 times. The organic layer was dried over anhydrous Na_2SO_4 and then removed solvent by evaporated in vacuum.

trans-2-Methoxycyclohexan-1-ol (**7**): yellow oil, ^{1}H-NMR ($CDCl_3$), δ (ppm): 3.39 (3H, s), 2.90-2.96 (1H, ddd, *J* = 4.3, 8.7, 10.8 Hz), 2.73 (1H, s), 2.10-2.13 (1H, m), 1.98-2.01 (1H, m), 1.68-1.74 (3H, m) and 1.02-1.29 (4H, m).

2.4 The general procedure for the ring opening of epoxides to halohydrins

Epoxide (1 mmol) was added to a solution of chromium catalyst (0.3 mmol) and additive, such as LiCl or LiBr, in THF (5 mL) in a round bottom flask and the mixture was stirred at reflux temperature for 5 min. After the reaction was completed, the reaction mixture was taken and diluted with Et_2O and then washed with distilled water 2 times. The organic layer was dried over anhydrous Na_2SO_4 and analyzed by GC with the addition of an exact amount of an appropriate internal standard.

1-Chlorododecan-2-ol (**9A**): colerless oil, ^{1}H-NMR ($CDCl_3$), δ (ppm): 3.76-3.80 (1H, m), 3.62-3.65 (1H, dd, *J* = 3.1, 11.0 Hz), 3.45-3.50 (1H, dd, *J* = 7.2, 11.0 Hz), 2.14 (1H, s), 1.44-1.53 (2H, m), 1.25 (16H, s) and 0.86-0.89 (3H, t, *J* = 6.6 Hz).

2-Chlorododecan-1-ol (**9B**): colerless oil, ^{1}H-NMR ($CDCl_3$), δ (ppm): 4.01-4.05 (1H, m), 3.76-3.82 (1H, m), 3.63-3.69 (1H, m), 2.00 (1H, s), 1.68-1.77 (2H, m), 1.59 (1H, s), 1.51-1.54 (1H, m), 1.43 (1H, m), 1.26 (13H, s) and 0.86-0.89 (3H, t, *J* = 6.6 Hz).

1-Bromododecan-2-ol (**10A**): colerless oil, ^{1}H-NMR ($CDCl_3$), δ (ppm): 3.76-3.76 (1H, m), 3.53-3.56 (1H, dd, *J* = 3.2, 10.3 Hz), 3.36-3.40 (1H, dd, *J* = 7.1, 10.3 Hz), 2.24 (1H, s), 1.53 (2H, m), 1.25 (16H, s) and 0.87 (3H, t, *J* = 6.5 Hz).

1-Bromo-3-butoxypropan-2-ol (**13**): yellow oil, ^{1}H-NMR ($CDCl_3$), δ (ppm): 3.93-3.98 (1H, quin, *J* = 5.3 Hz), 3.44-3.56 (6H, m), 2.59 (1H, br s), 1.52-1.59 (2H, quin, *J* = 6.7 Hz), 1.32-1.41 (2H, six, *J* = 7.4 Hz) and 0.90-0.94 (1H, t, *J* = 7.4 Hz).

1-Bromo-3-*tert*-butoxypropan-2-ol (**15**): yellow oil, ^{1}H-NMR ($CDCl_3$), δ (ppm): 3.91-3.87 (1H, m), 3.43-3.54 (4H, m), 2.65 (1H, br s) and 1.20 (9H, s).

1-Bromo-3-phenoxypropan-2-ol (**17**): yellow oil, ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.26-7.32 (2H, t, *J* = 7.9 Hz), 6.97-7.01 (1H, t, *J* = 7.3 Hz), 6.91-7.01 (2H, d, *J* = 8.3 Hz), 4.16-4.24 (1H, m), 4.06-4.14 (2H, m), 3.58-3.62 (1H, dd, *J* = 5.7, 10.4 Hz), 3.65-2.69 (1H, dd, *J* = 5.2, 10.4 Hz) and 2.59-2.60 (1H, s).

2-Chloro-2-phenylethanol (**19A**): light yellow oil, ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.30-7.42 (5H, m), 4.96-4.99 (1H, dd, *J* = 5.7, 7.4 Hz), 3.87-3.91 (1H, dd, *J* = 5.7, 12.0 Hz), 3.90-3.95 (1H, dd, *J* = 7.4, 12.0 Hz) and 2.82 (1H, s).

2-Chloro-1-phenylethanol (**19B**): light yellow oil, ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.38-7.39 (5H, d, *J* = 4.4 Hz), 4.88-4.90 (1H, dd, *J* = 3.5, 8.8 Hz), 3.71-3.75 (1H, dd, *J* = 3.5, 11.2 Hz), 3.62-3.67 (1H, dd, *J* = 8.8, 11.2 Hz) and 2.89 (1H, s).

2-Bromo-2-phenylethanol (**20A**): yellow oil, ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.30-7.38 (5H, d, *J* = 3.9 Hz), 4.88-4.91 (1H, dd, *J* = 3.6, 8.7 Hz), 3.60-3.63 (1H, dd, *J* = 3.6, 10.5 Hz), 3.51-3.55 (1H, dd, *J* = 8.8, 10.5 Hz) and 3.14 (1H, s).

2.5 The general procedure for the ring opening of epoxides with various amines to aminoalcohols

Cyclohexene oxide 0.101 mL (1 mmol) was added to a solution of chromium catalyst (0.5 mmol) and amines (5 mmol) in THF (5 mL) in a round bottom flask. The mixture was allowed to proceed at reflux temperature for 24 h with continuous stirring. After the reaction was completed, the reaction mixture was taken and diluted with Et_2O and then washed with distilled water 2 times. The organic layer was dried over anhydrous Na_2SO_4. The isolated yields were obtained gravimetrically after column chromatography with a gradient of 80/20 hexane/EtOAc. The identity and purity were determined by ^{1}H NMR. The product ratio was also obtained gravimetrically, or by GC if the separation was unsuccessful.

trans-2-(Benzylamino)cyclohexanol (**24**): yellow solid, ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.30-7.33 (4H, m), 7.23-7.27 (1H, m), 3.93-3.97 (1H, d, *J* = 12.9 Hz), 3.67-3.71 (1H, d, *J* = 12.9 Hz), 3.18-3.24 (1H, td, *J* = 4.7, 9.7 Hz), 2.45 (1H, br s), 2.27-2.33 (1H, ddd, *J* = 3.9, 9.4, 11.2 Hz), 2.14-2.17 (1H, m), 1.99-2.04 (1H, m), 1.71-1.74 (2H, m), 1.20-1.30 (3H, m) and 0.95-1.05 (1H, m).

trans-2-(Cyclohexylamino)cyclohexanol (**25**): white solid, ^{1}H-NMR ($CDCl_3$), δ (ppm): 3.06-3.12 (1H, td, *J* = 4.7, 9.7 Hz), 2.54-2.61 (1H, tt, *J* = 3.6, 10.2 Hz), 2.41 (1H, br s), 2.25-2.31 (1H, ddd, *J* = 3.8, 9.4, 11.2 Hz), 2.03-2.06 (2H, m), 1.89-1.92 (1H, m), 1.70-1.73 (5H, m), 1.57-1.60 (1H, m), 1.10-1.33 (7H, m) and 0.89-1.04 (2H, m).

trans-2-(Piperidino)cyclohexanol (**26**): yellow solid, ^{1}H-NMR ($CDCl_3$), δ (ppm): 3.94 (1H, s), 3.23-3.28 (1H, m), 2.56-2.60 (2H, m), 2.21-2.26 (2H, m), 2.02-2.07 (2H, m), 1.68-1.71 (2H, m), 1.60-1.61 (1H, m), 1.45-1.53 (4H, m), 1.35-1.36 (2H, m) and 1.00-1.20 (5H, m).

trans-2-(4-Chloroanilino)cyclohexanol (**28**): light brown solid, ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.10-7.12 (2H, d, *J* = 7.8 Hz), 6.62-6.64 (2H, d, *J* = 7.8 Hz), 3.32-3.38 (1H, td, *J* = 4.0, 9.5 Hz), 2.98-3.11 (1H, td, *J* = 3.7, 10.0 Hz), 2.59 (1H, br s), 2.07-2.13 (2H, m), 1.71-1.73 (2H, m), 1.24-1.43 (3H, m) and 1.00-1.11 (1H, m).

trans-1,2-Cyclohexandiol (**30**): white solid, ^{1}H-NMR ($CDCl_3$), δ (ppm): 3.35 (2H, s), 2.63 (1H, br s), 2.37 (1H, br s), 1.96 (2H, s), 1.70 (2H, s) and 1.26 (4H, s).

trans-2-(Naphthylamino)cyclohexanol (**32**): orange solid, ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.81-7.87 (2H, m), 7.46-7.48 (2H, m), 7.26-7.38 (2H, m), 6.77-6.83 (1H, m), 3.52-3.58 (1H, td, *J* = 4.2, 9.7 Hz), 3.35-3.40 (1H, td, *J* = 3.7, 10.3 Hz), 2.24-2.27 (1H, d, *J* = 13.1 Hz), 2.16-2.19 (1H, d, *J* = 13.1 Hz), 1.74-1.82 (2H, m), 1.32-1.49 (3H, m) and 1.09-1.17 (1H, m).

2.6 The general procedure for the ring opening of epoxides with aniline to aminoalcohols

Epoxide (1 mmol) was added to a solution of $Cr(NO_3)_3.9H_2O$ (0.1 mmol) and aniline (5 mmol) in THF (5 mL) in a round bottom flask. The mixture was then refluxed for 6 h with continuous stirring. After the reaction was completed, the reaction mixture was taken and diluted with Et_2O and then washed with distilled water 2 times. The organic layer was dried over anhydrous Na_2SO_4 then evaporated in vacuum to obtain product. The isolated yields were obtained gravimetrically after column chromatography with a gradient of 80/20 hexane/EtOAc. The identity and purity were determined by ^{1}H NMR.

2-Anilino-2-phenyl-1-ethanol (**33A**): yellow liquid, ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.18-7.30 (5H, m), 7.01-7.05 (2H, t, *J* = 7.8 Hz), 6.59-6.62 (1H, t, *J* = 7.3 Hz), 6.49-6.51 (2H, d, *J* = 7.85 Hz), 4.42-4.44 (1H, dd, *J* = 4.2, 6.8 Hz), 3.85-3.88 (1H, dd, *J* = 4.2, 11.1 Hz), 3.66-3.70 (1H, dd, *J* = 6.9, 11.1 Hz) and 2.09 (1H, s).

1-Anilino-2-dodecanol (**34A**): yellow liquid, ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.17-7.20 (2H, dd, *J* = 7.5, 8.4 Hz), 6.72-6.75 (1H, t, *J* = 7.3 Hz), 6.65-6.67 (2H, d, *J* = 7.7 Hz), 3.80-3.86 (1H, m), 3.25-3.29 (1H, dd, *J* = 3.1, 12.9 Hz), 2.97-3.03 (1H, dd, *J* = 8.6, 12.9 Hz), 2.02 (2H, br s), 1.51-1.56 (2H, m), 1.26 (16H, br s) and 0.86-0.90 (3H, t, *J* = 6.7 Hz).

2.7 Study on the optimum conditions for the ring opening of cyclohexene oxide to halohydrin

2.7.1 Effect of type of metal chloride

The ring opening of cyclohexene oxide was carried out employing $CrCl_3.6H_2O$, $InCl_3.H_2O$, $CoCl_2$, $CuCl_2$, $NiCl_2$, $MnCl_2$ or $FeCl_3$ as reagent.

2.7.2 Effect of solvent

The ring opening of cyclohexene oxide was carried out in the same manner as previously described but changing the reaction medium from THF to various solvents, namely cyclohexane, CH_3CN, CH_2Cl_2, EtOAc, hexane and toluene.

2.7.3 Effect of the amount of $CrCl_3.6H_2O$

The ring opening of cyclohexene oxide was carried out in the same fashion as previously described using different amounts of $CrCl_3.6H_2O$ (0.1, 0.3, 0.5 and 1 mmol).

2.7.4 Kinetic study

The ring opening of cyclohexene oxide was performed according to the general procedure mentioned earlier using $CrCl_3.6H_2O$ or $Cr(NO_3)_3.9H_2O$, but different reaction temperatures (room temperature, reflux temperature) and reaction times (10, 20, 30 min and 1 h) were varied.

2.7.5 Effect of additives

The ring opening of cyclohexene oxide was performed in the same fashion as previously described using $CrCl_3.6H_2O$ or $Cr(NO_3)_3.9H_2O$. Various additives such as LiCl, LiBr and LiI were varied.

2.7.6 Effect of CH_3OH additives

The ring opening of cyclohexene oxide was performed according to the general procedure mentioned earlier using $Cr(NO_3)_3.9H_2O$. CH_3OH was selected as other additives to add to the reaction.

2.7.7 Study on reactivity of halide nucleophile

The ring opening of cyclohexene oxide was carried out in the same manner as previously described by adding $CrCl_3.6H_2O/CrBr_3$ as reagent or LiCl/LiBr as additive to the reaction in order to study the competitive reactivity of nucleophile.

2.8 Ring opening of various selected epoxides to halohydrins

Selected epoxides including 1-dodecene oxide, butyl glycidyl ether, *tert*-butyl glycidyl ether, phenyl glycidyl ether, styrene oxide, *trans*-stilbene oxide (1 mmol each) were subjected to this developed ring opening system using chromium reagents and halide additive. Other procedures were carried out as previously described.

2.9 Study on the optimum conditions for the ring opening of cyclohexene oxide to aminoalcohol

2.9.1 Effect of solvent

The ring opening of cyclohexene oxide with aniline was carried out in the same manner as previously described but changing the reaction medium from THF to cyclohexane.

2.9.2 Effect of the amount of substrate

The ring opening of cyclohexene oxide was carried out employing $CrCl_3.6H_2O$ and aniline using different amounts of cyclohexene oxide (0.5 and 1 mmol).

2.9.3 Effect of amount of aniline nucleophile

The ring opening of cyclohexene oxide was carried out using different amounts of aniline (1.1, 3, 5 and 10 mmol).

2.9.4 Effect of the amount of $CrCl_3.6H_2O$

The ring opening of cyclohexene oxide was carried out employing $CrCl_3.6H_2O$ and aniline using different amounts of $CrCl_3.6H_2O$ (0.05 and 0.1 mmol).

2.9.5 Kinetic study

The ring opening of cyclohexene oxide was performed according to the general procedure mentioned earlier using $CrCl_3.6H_2O$ or $Cr(NO_3)_3.9H_2O$ and aniline with different reaction times (30 min, 1, 3 and 6 h).

2.9.6 Effect of the amount of $Cr(NO_3)_3.9H_2O$

The ring opening of cyclohexene oxide was carried out employing $Cr(NO_3)_3.9H_2O$ and benzylamine using different amounts of $Cr(NO_3)_3.9H_2O$ (0.05 and 0.1 mmol).

2.10 Ring opening of epoxide to aminoalcohol with various amine nucleophiles

Selected nucleophiles including cyclohexylamine, piperidine, diethylamine, benzylamine, *p*-chloroaniline, *p*-nitroaniline, *N*-methylaniline (5 mmol each) were selected as a nucleophile in this developed ring opening system employing chromium reagents. Other procedures were carried out as previously described.

2.11 Ring opening of various selected epoxides to aminoalcohols

Selected epoxides including 1-dodecene oxide and styrene oxide (1 mmol each) were subjected to this developed ring opening system using chromium reagents and amine nucleophile. Other procedures were carried out as previously described.

2.12 General isolation procedure

After the reaction was completed (followed by TLC), the transformed product was separated as follows: the whole reaction mixture was extracted according to that described in the general procedure and all solvents were removed. The crude product was purified by silica gel column using a mixture of hexane-EtOAc as an eluent. The equivalent fractions monitored by TLC were combined and the solvents were completely evaporated.

CHAPTER III

RESULTS AND DISCUSSION

The transformations of epoxides into halohydrins and aminoalcohols are well recognized as one of important industrial processes. Several reagents have consequently been developed and utilized for this purpose. For instance, LiBr/Amb15 [22], $CoCl_2$ [28, 30], $BiCl_3$ [29] and $Al(OTf)_3$ [32].

Among transition metal-mediated ring opening of epoxides, only a few reports concerned with the use of chromium salts and complexes. Thus, this research was focused on the utilization of chromium reagents in epoxide ring opening. The methodology towards the transformation of epoxides to more valuable and widely useful products with high yield and good selectivity was explored. Advantages of this method include the highly catalytic nature of the reagent, low cost, commercially available, rapid reaction rate and insensitivity to air and moisture.

Cyclohexene oxide (**1**) was selected as a model substrate for reaction conditions optimization. For the experiments towards halohydrins formation, the system generally composed of cyclohexene oxide, solvent such as THF and chromium salt or complex as a reagent. Other substrates including 1-dodecene oxide, butyl glycidyl ether, *tert*-butyl glycidyl ether, phenyl glycidyl ether, styrene oxide, *trans*-stilbene oxide and methyl *trans*-3-(4-methoxyphenyl)-glycidate were selected as chemical probes to observe the regioselectivity of the reaction. For aminoalcohols synthesis, amine is another reagent added into the system. Aniline was chosen as a primary model. In addition, various amines including benzylamine, cyclohexylamine, piperidine, diethylamine, methylphenylamine, 4-chloroaniline and 4-nitroaniline were chosen to examine the role of steric and electronic effects of nucleophile. Morover, other substrates including 1-dodecene oxide and styrene oxide were selected as chemical probes to observe the regioselectivity of this reaction. To our best knowledge the utilization of chromium salts and complexes, particularly $CrCl_3.6H_2O$

and $Cr(NO_3)_3.9H_2O$ have never been reported in chemical literature for these kinds of transformation.

3.1 The optimum conditions for the transformation of cyclohexene oxide

Generally, various factors are needed to be evaluated to optimize the transformation explored such as type of metal halides, type and amount of chromium salt and complex, atmosphere, time and temperature. Within the scope of this preliminary investigation, cyclohexene oxide (**1**), a primary chemical model was reacted with chromium reagents furnishing *trans*-2-chlorocyclohexanol (**2**) as a product. While adding aniline as an external nucleophile, *trans*-2-(phenylamino)cyclohexanol (**23**) was obtained as a major product. This desired product is commonly used in manufacturing of pharmaceuticals, insecticides, fungicides, herbicides and could become a useful intermediate in many organic syntheses of industrial interest.

In this study, the experimental was divided into two parts. The first was the study on the optimum conditions for the transformation of epoxide to halohydrin and the second was to aminoalcohol.

Part I : Transformation of epoxide to halohydrin

To verify the identity of the desired product, ^{1}H-NMR spectroscopy was utilized. The ^{1}H-NMR spectrum of *trans*-2-chlorocyclohexanol (**2**) (Fig 3.1) reveals the hydroxy proton at δ_H 2.74 (1H, br s). The α-proton could be assigned at δ_H 3.66-3.72 (1H, td, J = 4.2, 10.1 Hz), whereas that at the carbon connecting with chlorine atom could be visualized at δ_H 3.47-3.50 (1H, td, J = 4.3, 9.1 Hz). The ^{13}C-NMR spectrum (Fig 3.2) displays the α-carbon at δ_C 75.1. The carbon connecting with chlorine atom was detected at δ_C 67.2 and the others at δ_C 35.1, 33.2, 25.5 and 23.9 indicating methylene carbons.

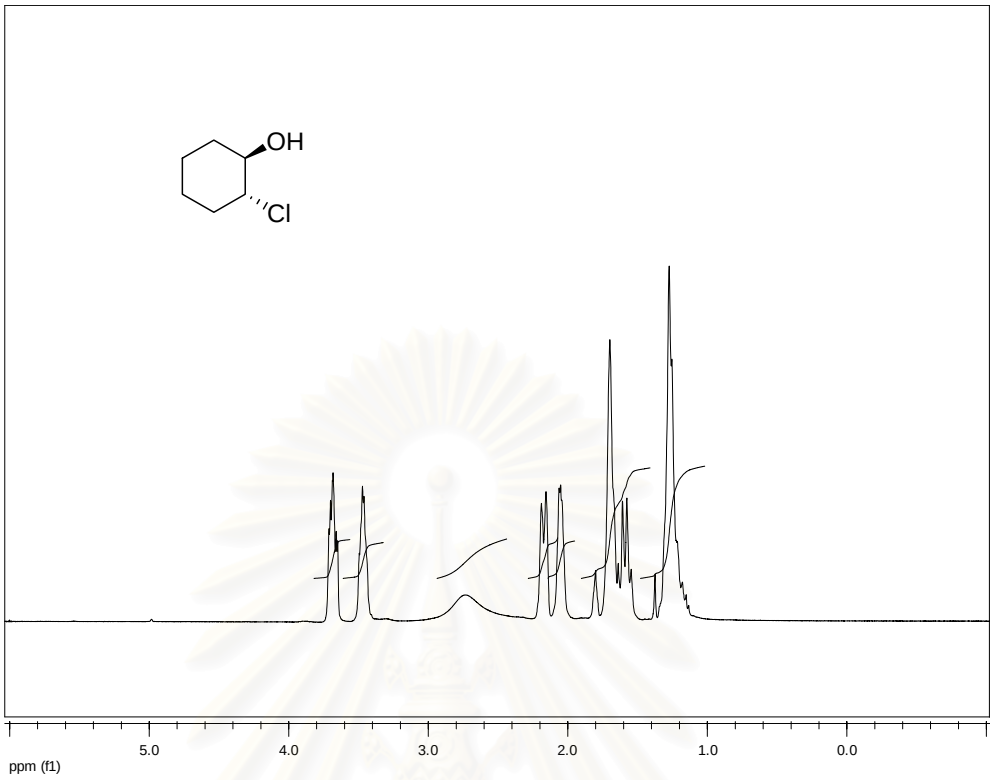


Figure 3.1 The ^{1}H-NMR spectrum of *trans*-2-chlorocyclohexanol (**2**)

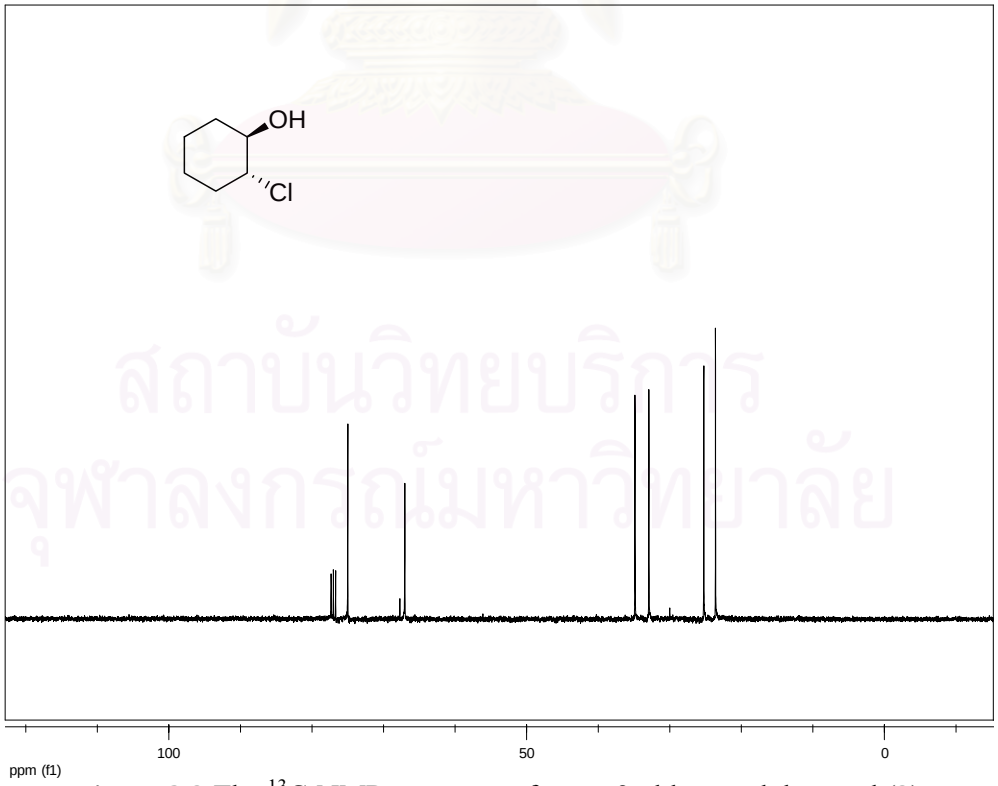
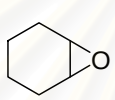


Figure 3.2 The ^{13}C-NMR spectrum of *trans*-2-chlorocyclohexanol (**2**)

3.1.1 Effect of type of metal halide on cyclohexene oxide transformation to halohydrin

The transformation of epoxides utilizing metal halide was emerging as a synthetically useful protocol and effective as explicitly seen from many successful reports [22, 28-30]. Although there have been some investigations on the use of metal complexes for transformation of epoxides, there was no report of utilizing $CrCl_3 \cdot 6H_2O$ as a reagent. The goal of this study was thus focused on screening of metal halides for the epoxide ring opening. Under this particular condition, the ring opening of cyclohexene oxide (**1**) provided *trans*-2-chlorocyclohexanol **(2)** as a product. The effects of metal halide on cyclohexene oxide ring opening are consequently examined and the results are presented in Table 3.1.



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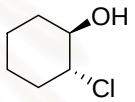


2

Table 3.1 Effect of metal halide on cyclohexene oxide ring opening

Entry	Metal halide	% yield		MB
		recovered 1	2	
1	none	100	0	100
2	$CrCl_3.6H_2O$	0	97	97
3	$InCl_3.H_2O$	100	1	101
4	$CoCl_2$	71	24	95
5	$CuCl_2$	50	49	99
6	$NiCl_2$	99	0	99
7	$MnCl_2$	98	0	98
8	$NiBr_2.3H_2O$	42	60*	102

Reaction conditions: cyclohexene oxide 1 mmol, metal halide 1 mmol, THF 5 mL, room temperature (30ºC), 30 min

*yield of *trans*-2-bromocyclohexanol

The observations obtained from Table 3.1 provided an interesting result. A blank experiment clearly revealed that in the absence of metal halide, no reaction was

occurred. Under standard conditions, only a few metal halides chosen influenced the transformation. Those including $CoCl_2$, $CuCl_2$ and $NiBr_2.3H_2O$ could assist the ring opening of cyclohexene oxide (**1**) yielding the corresponding halohydrin in low to moderate yield (entries 4, 5, 8). In addition, other metal halides could not assist the cyclohexene oxide transformation, for instance $InCl_3.H_2O$, $NiCl_2$ and $MnCl_2$ (entries 3, 6, 7). $CrCl_3.6H_2O$ seemed to be the highest efficient reagent for cyclohexene oxide transformation yielding **2** (entry 2). Thus, in this research $CrCl_3.6H_2O$ was selected as a reagent for further investigation.

3.1.2 Effect of solvent on cyclohexene oxide ring opening by $CrCl_3.6H_2O$

Solvents always play an important role to control the selectivity of the reaction. Among several diverse solvents studied, THF was the first solvent chosen as a reaction medium because it could dissolve both chromium reagent and a substrate. However, in this study several solvents were tried to evaluate their compatibility with $CrCl_3.6H_2O$ in the ring opening of cyclohexene oxide and to observe whether they could replace THF. According to many reports, several solvents for example cyclohexane [33], CH_2Cl_2 [19, 21, 34], toluene [35] and CH_3CN [36] were successfully applied as the solvent system for epoxide ring opening reaction. In this study, the variation of selected solvents such as cyclohexane, CH_2Cl_2, EtOAc, hexane, toluene and CH_3CN in the transformation of cyclohexene oxide using $CrCl_3.6H_2O$ is applied.

Gaining the information from the experimental results, $CrCl_3.6H_2O$ could not be homogeneously dissolved in most kinds of solvent. Non-polar solvents such as hexane, cyclohexane and toluene served as a non-suitable solvent and displayed low efficiency yielding the target product in low yield. This same result was also obtained using slightly polar solvent as EtOAc and CH_2Cl_2. The polar solvent CH_3CN gave 26% yield of the desired product. However, it still gave the lower yield compared with THF of which the yield was 97%. It seemed that the polarity and the dielectric constant of the solvent did not have any close correlation with the transformation of epoxide.

From this study, THF still displayed the best compatibility with $CrCl_3.6H_2O$ and most suitable to furnish the high yield of halohydrin. Similarly as reported for the ring opening of epoxide, THF was chosen to use as solvent in most systems of this kind of reaction [37, 38].

3.1.3 Effect of the amount of $CrCl_3.6H_2O$ on transformation of cyclohexene oxide

Another plausible parameter that may affect the outcome of the reaction was the amount of $CrCl_3.6H_2O$. The effect of the amount of $CrCl_3.6H_2O$ on cyclohexene oxide transformation was examined and the results are tabulated as shown in Table 3.2.

Table 3.2 Effect of the amount of reagent on cyclohexene oxide ring opening

Entry	$CrCl_3 \cdot 6H_2O$ (mmol)	% yield		MB
		recovered 1	2	
1	0	104	0	104
2	0.1	88	15	103
3	0.3	53	51	104
4	0.5	17	85	102
5	1.0	0	97	97

Reaction conditions: cyclohexene oxide 1 mmol, THF 5 mL, room temperature (30ºC), 30 min

Table 3.2 clearly reveals that the dependence on the amount of $CrCl_3.6H_2O$ was directly influenced on the outcome of the transformation of cyclohexene oxide. The more amount of $CrCl_3.6H_2O$ was used, the better yield of *trans*-2-chlorocyclohexanol (**2**) was obtained. The maximum yield of the desired product was obtained (entry 5) when 1.0 mmol of $CrCl_3.6H_2O$ was used. This result was consistent with previous studies that the increasing yield appeared to be largely dependent on the amount of catalyst [21, 39].

3.1.4 Kinetic study on cyclohexene oxide transformation by $CrCl_3.6H_2O$

Although $CrCl_3.6H_2O$ 1.0 mmol was the most efficient reagent, the stoichiometric amount was required. With the aim to maximize the yield of the desired product while to minimize the amount of $CrCl_3.6H_2O$, a kinetic study on cyclohexene oxide transformation was compared using 0.1, 0.3 and 1.0 mmol of $CrCl_3.6H_2O$ at room and reflux temperature. The results are collected in Fig 3.3.

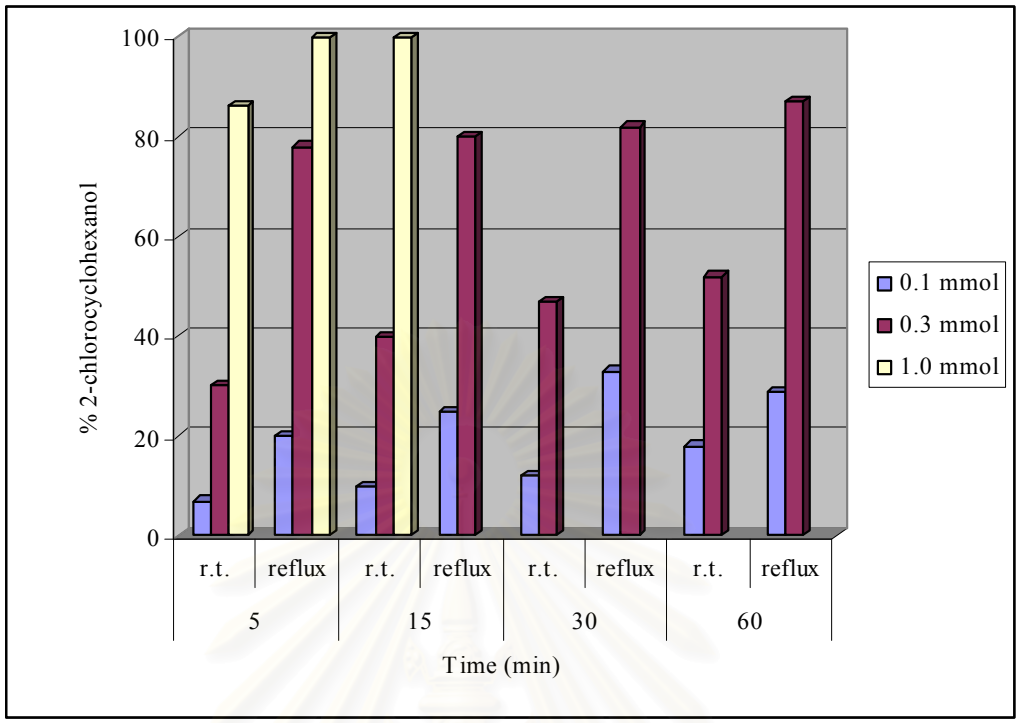


Figure 3.3 Kinetic study on the transformation of cyclohexene oxide (**1**) at room and reflux temperature

The results from Fig 3.3 demonstrate that the transformation of cyclohexene oxide into chlorohydrin was probably depending on the amount of chloride ion source presented in the reaction.

At room temperature, the transformation of cyclohexene oxide (**1**) by 0.1 mmol of $CrCl_3.6H_2O$ yielded **2** in low yield even if the reaction time was increased. When the amount of $CrCl_3.6H_2O$ was increased to 0.3 mmol, the increasing of reaction time affected on the increment yield of the desired product. The chlorohydrin (**2**) was obtained in moderate yield at 1 h. The transformation of cyclohexene oxide (**1**) using 1 mmol of $CrCl_3.6H_2O$ was completed within 15 min.

At reflux temperature, the same trend of the results was acheived. $CrCl_3.6H_2O$ 0.1 mmol still provided **2** in low yield even if the reaction time increased. $CrCl_3.6H_2O$ 0.3 mmol was also affected on the increment of the yield of the desired product. As noticed from the results, the yield of the product when the reaction time was 30 min was comparable with that at 1 h. Employing 1 mmol of $CrCl_3.6H_2O$, the quantitative yield of *trans*-2-chlorocyclohexanol could be achieved within 5 min.

It could thus be summarized that the increasing of chloride ion source presenting in the reaction was the important factor to raise the yield of product. The advantage of this developed system was that the reaction could furnish the desired product in excellent yield with a short period of time.

According to the above results, $CrCl_3.6H_2O$ 0.1 and 0.3 mmols were selected for further investigation with the aim to reduce the reagent but still keep the efficiency of the reaction.

3.1.5 Effect of the amount of LiCl and temperature on cyclohexene oxide transformation

Stemmed from the results attained above, the use of $CrCl_3.6H_2O$ 0.1 or 0.3 mmol for 30 min at refluxing THF could not make the reaction complete. The extra chloride ion source may need to enhance this underplay reaction.

Among the myriad of nucleophiles that have been employed in ring openings, the classical reagents for halohydrin synthesis are strong Lewis or hydrohalic acids [40], which provided powerful electrophilic activation. However, these procedures are associated with the disadvantages of intolerance to acid-sensitive moieties and by-product formation [41]. Metal halides such as LiX [42] and $TiCl_4$·LiX [43] complexes have been recently reported for this transformation even though an excess of reagent was required and particularly in the case of chlorohydrins which took several days for complete conversion. The hygroscopic nature of LiI limited its use in making iodohydrins. However, many methods based upon LiX have considerable been reported for this reaction [37]. In this study, LiX such as LiCl was selected to assist the reaction because of its good solubitity in THF. The effect of this extra additive, when $CrCl_3.6H_2O$ 0.1 and 0.3 mmol were used, is presented in Fig 3.4.

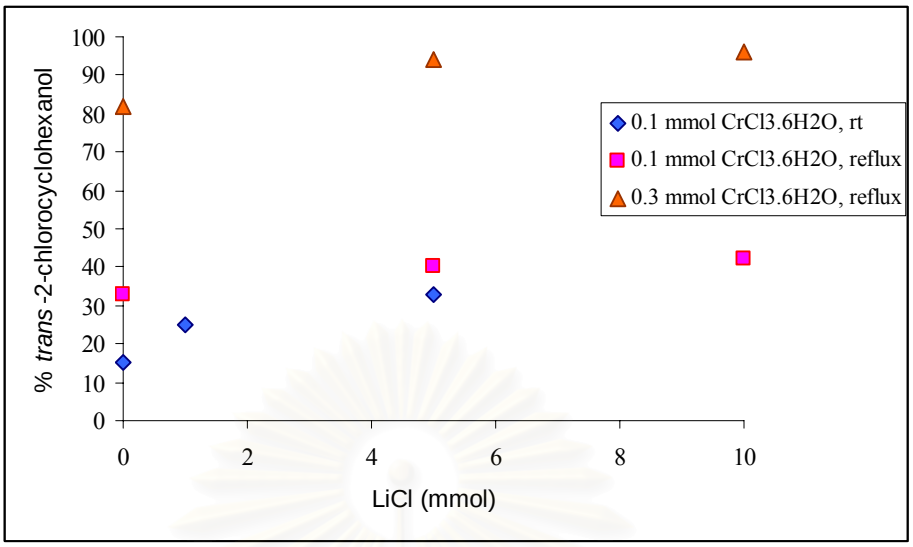


Figure 3.4 Effect of LiCl and kinetic study on the transformation of cyclohexene oxide (**1**) at room temperature and reflux temperature

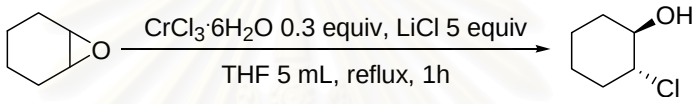
Fig 3.4 displays various intriguing points. When the more LiCl was added, the more chlorohydrin was attained. Utilizing $CrCl_3.6H_2O$ 0.1 mmol at room temperature, LiCl 1 and 5 mmol furnished the desired product 26% and 36%, respectively. It seemed that LiCl could succor to gain the increasing amount of product possibly due to the fact that LiCl could release the chloride ion to assist the ring opening reaction; however still low yield. Therefore, the attempt to increase the desired product was to rise up the reaction temperature.

At reflux temperature, when the amount of $CrCl_3.6H_2O$ 0.1 mmol was used, LiCl 5 or 10 mmol was added in the reaction. The moderate yields of chlorohydrin approximately 40% and 42%, respectively were obtained. In case of using $CrCl_3.6H_2O$ 0.3 mmol, it was however indifferent in terms of the product yield when using additive LiCl 5 or 10 mmol. The reason of this point could explain by the solubility of LiCl in THF. LiCl 5 mmol was completely soluble in THF while LiCl 10 mmol was solute only some parts which affected the reaction medium not be homogeneous. Therefore, it seemed to obtain comparable amount of chloride ion source existed in the reaction either LiCl 5 or 10 mmol were used.

It could be concluded that LiCl 5 mmol was the best amount that could assist the reaction. The increasing of LiCl more than 5 mmol did not yield more products. However, the reaction was still not completed within 30 min. Therefore, the increasing of reaction time was needed to complete the reaction.

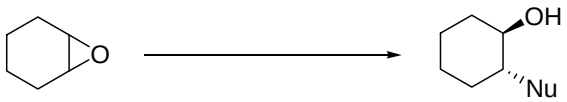
When the reaction time was left for 1 h, the conversion was completed and the quantitative yield of product was obtained. From this result, an extra amount of LiCl could assist this transformation successfully.

From the outcome of variable factors studied as described above, it could be concluded that the optimum conditions for the transformation of cyclohexene oxide in the homogeneous system are as follows: cyclohexene oxide 1 mmol as a substrate, $CrCl_3.6H_2O$ 0.3 mmol as a reagent, additive LiCl 5 mmol in THF 5 mL at reflux for 1 h. The quantitative yield of the corresponding *trans*-2-chlorocyclohexanol (**2**) was attained. These conditions were applied as standard conditions for further investigation.



3.1.6 Effect of other halide additives on cyclohexene oxide transformation using $CrCl_3.6H_2O$

Several extra additives were tried in order to find more efficient additives to furnish the varieties of halohydrins. LiBr and LiI were chosen to study for bromo- and iodohydrins formation, respectively. Other additive, for example NaX, was reported to use as halogenating agent [44]. Therefore, in this study, the exploration of type of external halides: NaCl, NH_4Cl, LiBr and LiI was conducted using $CrCl_3.6H_2O$. The results are tabulated as shown in Table 3.3.



Nu = Br (**3**), I (**4**)

Table 3.3 Effect of various halide additives on cyclohexene oxide ring opening

Entry	Additive (5 mmol)	%		MB
		recovered 1	product	
1	LiCl	-	**2** (103)	103
2	NaCl	9	**2** (91)	100
3	NH_4Cl	13	**2** (87)	100
4	LiBr	-	**2** (2), **3** (99)	101
5	LiI	-	**4** (100)	100

Reaction conditions: cyclohexene oxide 1 mmol, $CrCl_3.6H_2O$ 0.3 mmol, additive 5 mmol, THF 5 mL, reflux (70°C), 1 hr

From Table 3.3, it was clearly seen that NaCl and NH_4Cl could also be used in this reaction; however the solubility of LiCl seemed to be superior than the others that made the conversion using LiCl better (entries 1-3). The corresponding bromohydrin could be attained when LiBr was used in excellent yield with small amount of chlorohydrin as a side product (entry 4). In addition, iodohydrin was obtained when LiI was used in quantitative yield (entry 5).

The ^{1}H-NMR spectrum of *trans*-2-bromocyclohexanol (**3**) (Fig A1) revealed the hydroxy proton at δ_H 2.66 (1H, s). The proton beside to a hydroxyl group at δ_H 3.85-3.91 (1H, ddd, J = 4.2, 9.4, 11.8 Hz) and that on the carbon connecting with bromine atom could be visualized at δ_H 3.55-3.61 (1H, td, J = 4.5, 9.8 Hz). The methylene protons could be assigned at δ_H 2.29-2.35 (1H, m), 2.09-2.12 (1H, m), 1.65-1.87 (3H, m) and 1.20-1.40 (3H, m).

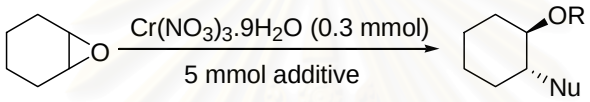
The ^{1}H-NMR spectrum of *trans*-2-iodocyclohexanol (**4**) (Fig A2) revealed the proton beside to a hydroxyl group at δ_H 4.00-4.08 (1H, td, J = 4.1, 10.9 Hz), whereas those at carbon connecting with iodide could be visualized at δ_H 3.63-3.67 (1H, td, J = 4.3, 9.9 Hz). The methylene protons could be assigned at δ_H 2.45-2.56 (1H, m), 2.23-2.36 (1H, m), 1.71-2.13 (3H, m) and 1.20-1.53 (3H, m).

According to the results above, LiX showed high efficiency as external nucleiphile in the transformation of epoxide to halohydrin. However, in the case of

bromohydrin formation, by-product chlorohydrin was also observed due to $CrCl_3.6H_2O$ reagent. The further investigation aimed to avoid this side product was explored.

3.1.7 Effect of various halide additives on cyclohexene oxide ring opening using $Cr(NO_3)_3.9H_2O$

To avoid the chlorohydrin formation which derived from $CrCl_3.6H_2O$, $Cr(NO_3)_3.9H_2O$ was chosen. The exploration of type and kinetic study of external halides: LiCl, NaCl, NH_4Cl, LiBr and LiI were thus conducted using $Cr(NO_3)_3 \cdot 9H_2O$. The results are tabulated as shown in Table 3.4.



Nu = Cl, R = H (**2**)
Nu = Br, R = H (**3**)
Nu = I, R = H (**4**)
Nu = ONO_2, R = H (**5**)
Nu = ONO_2, R = C_4H_8OH (**6**)

Table 3.4 Effect of various additives on cyclohexene oxide ring opening using $Cr(NO_3)_3.9H_2O$

Entry	Additive	Time (min)	%		MB
			recovered 1	product	
1	-	60	10	**5** (82), **6** (4)	96
2	NaCl	60	9	**2** (9), **5** (66), **6** (3)	87
3	NH_4Cl	60	16	**2** (16), **5** (64), **6** (3)	99
4	LiCl	60	0	**2** (104)	104
5	LiCl	30	4	**2** (101)	105
6	LiCl	15	8	**2** (94)	102
7	LiCl	5	8	**2** (92)	100
8	LiBr	60	0	**3** (99)	99
9	LiBr	30	0	**3** (100)	100
10	LiBr	15	0	**3** (102)	102
11	LiBr	5	0	**3** (105)	105

Table 3.4 (continued)

Entry	Additive	Time (min)	%		MB
			recovered 1	product	
12	LiI	60	1	**4** (99)	100
13	LiI	30	5	**4** (96)	101
14	LiI	15	4	**4** (96)	100
15	LiI	5	7	**4** (95)	102

Reaction conditions: cyclohexene oxide 1 mmol, $Cr(NO_3)_3.9H_2O$ 0.3 mmol, additive 5 mmol, THF 5 mL, reflux (70°C)

From Table 3.4, without any additive (entry 1), the reaction mainly took place with the cleavage of epoxide to nitrate ester, *trans*-2-nitroxycyclohexan-1-ol, **5**. Interestingly, this method was another procedure to synthesize the nitrate ester which in fact has many advantages in organic synthesis. Nitrate esters found widespread therapeutically importance as drugs for treatment of heart and vascular diseases [45]. The minor product obtained from this reaction was an unknown compound. After being carefully isolated this compound by silica gel column, it was confirmed by ^{1}H-NMR spectroscopy to be the derivative of the THF ring opening, *trans*-4-(2-nitrooxycyclohexyloxy)-butan-1-ol (**6**).

The ^{1}H-NMR spectrum of *trans*-2-nitroxycyclohexan-1-ol (**5**) (Fig A3) displayed the signal of the proton on the carbon next to a hydroxyl group at δ_H 3.61-3.67 (1H, td, J = 4.8, 9.9 Hz). The protons on the carbon adjacent to a nitrate group were visualized at δ_H 4.77-4.83 (1H, td, J = 4.6, 9.7 Hz). The methylene protons could be assigned at δ_H 2.04-2.18 (3H, m), 1.74-1.77 (2H, m) and 1.23-1.48 (3H, m). The ^{13}C-NMR spectrum of **5** (Fig A4) displayed two signals at δ_C 70.5 and 87.3 indicating the carbons connecting to hydroxy and nitrate groups, respectively. The methylene carbons in a cyclic ring were detected at δ_C 33.0, 28.7, 23.8 and 23.4.

The ^{1}H-NMR spectrum of *trans*-4-(2-nitrooxycyclohexyloxy)-butan-1-ol (**6**) (Fig A5) revealed the hydroxy proton at δ_H 2.62 (1H, br s). The proton on the carbon next to a hydroxyl group at δ_H 4.46-4.49 (2H, t, J = 6.5 Hz). The protons adjacent to a nitrate group were visualized at δ_H 3.62-3.67 (1H, dt, J = 6.3, 9.3 Hz). The protons of a cyclic and long chain carbons connecting with ether oxygen atom could be assigned at δ_H 2.98-3.04 (1H, ddd, J = 4.2, 8.8, 10.4 Hz) and 3.37-3.43 (2H, dt, J = 5.9, 9.3

Hz), respectively. The methylene protons could be assigned at δ_H 1.98-2.00 (1H, m), 2.04-2.07 (1H, m), 1.78-1.85 (2H, m), 1.65-1.72 (4H, m) and 1.05-1.32 (4H, m). The ^{13}C-NMR spectrum of **6** (Fig A6) displayed two peaks at δ_C 73.8 and 67.7 indicating the carbons connecting to hydroxy and nitrate groups, respectively. The carbons besides the ether oxygen atom of a cyclic and long chain carbons displayed at δ_C 83.7 and 73.1, respectively. Methylene carbons of a cyclic were detected at δ_C 32.0, 29.0, 24.2 and 23.9 whereas long chain carbons were visualized at δ_C 26.3 and 23.9.

The structure of this compound was indeed confirmed by ^{1}H-, ^{13}C-NMR, COSY (Fig A8), HMQC (Fig A9) and HMBC (Fig A10). The tentative chemical shift assignments of this compound are tabulated in Table 3.5.

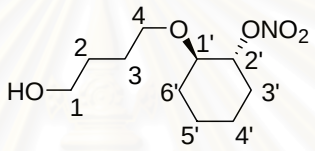


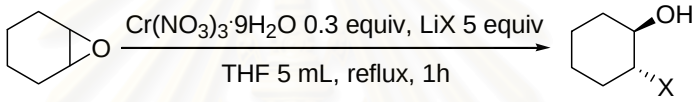
Table 3.5 The ^{1}H and ^{13}C-NMR chemical shift assignment of Compound **6**

Position	Compound **6**		COSY	HMBC (C-H)
	δ_C	δ_H (mult. in Hz)		
1	73.1	4.46-4.49 (2H, t, 6.5)	2	1, 3
2	26.3	1.78-1.85 (2H, m)	1, 3	2, 4, 1'
3	23.9	1.65-1.72 (2H, m)	2, 6',	1, 1'
4	73.8	3.37-3.43 (2H, dt, *J* = 5.9, 9.3)	3, 2', 6'	2, 2', 6'
1'	67.7	3.62-3.67 (1H, dt, *J* = 6.3, 9.3)	4, 5'	4', 5'
2'	83.7	2.98-3.04 (1H, ddd, 4.2, 8.8, 10.4)	4, 3'	4, 6'
3'	29.1	2.04-2.07 (1H, m), 1.05-1.32 (1H, m)	2', 4'	5'
4'	23.9	1.65-1.72 (1H, m), 1.05-1.32 (1H, m)	3', 5', 6'	1', 4
5'	24.2	1.65-1.72 (1H, m), 1.05-1.32 (1H, m)	3', 4', 6'	3'
6'	32.0	1.98-2.00 (1H, m), 1.05-1.32 (1H, m)	4', 5'	4, 4', -OH
-OH	-	2.62 (1H, br s)	-	-

According to the results presented in Table 3.4, NaCl and NH_4Cl were tested as an extra additive. The reaction was however not selective and furnished low yield of the desired chlorohydrins (entries 2-3). LiCl was another additive that could assist

the reaction to achieve chlorohydrin in high yield and the reaction was completed within 1 h (entries 4-7). LiBr revealed the sufficient reactivity to furnish the desired bromohydrin in quantitative yield within only 5 min (entries 8-11). In addition, LiI was also reactive to provide iodohydrin in quantitative yield (entries 12-15) within 5 min.

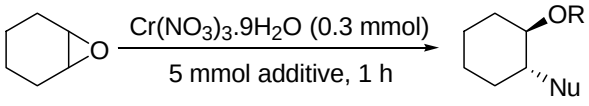
From the above result, it can be summarized that the optimum conditions for the selective transformation of cyclohexene oxide into halohydrin are as follows: cyclohexene oxide 1 mmol as a substrate, $Cr(NO_3)_3.9H_2O$ 0.3 mmol as a reagent, LiX as an additive 5 mmol and THF 5 mL as a solvent at reflux for 1 h. The quantitative yield of the corresponding *trans*-2-halocyclohexanol was obtained. Therefore, these conditions were applied as standard protocol for further investigation.



3.1.8 Effect of CH_3OH on cyclohexene oxide ring opening by $Cr(NO_3)_3.9H_2O$

β-Alkoxyalcohols constitute an important class of organic compounds and can be used as intermediates for the preparation of α-alkoxyketones and α-alkoxy acids as well as for the synthesis of compounds with pharmaceutical interest [46]. The main protocol for the synthesis of β-alkoxyalcohols is the alcoholysis of 1,2-epoxides [47]. In this study, CH_3OH was selected as a simple nucleophile to synthesize methoxyalcohol assisted by $Cr(NO_3)_3.9H_2O$.

Under the optimized conditions as discussed above, the reaction was carried out using CH_3OH as a nucleophile. The outcome of the transformation of cyclohexene oxide is summarized in Table 3.6.



(**1**)

Nu = ONO_2, R = H (**5**)
Nu = ONO_2, R = C_4H_8OH (**6**)
Nu = OCH_3, R = H (**7**)

Table 3.6 Effect of CH_3OH on cyclohexene oxide ring opening

Entry	Amount of CH_3OH	%		MB
		recovered 1	product	
1	-	100	-	100
2	10 mmol	4	**5** (89), **6** (3), **7** (9)	105
3[a]	5 mL	-	**5** (19), **7** (78)	97
4[b]	5 mL	-	**5** (12), **6** (1), **7** (86)	99
5[b]	10 mL	-	**7** (102)	102

Reaction conditions: cyclohexene oxide 1 mmol, $Cr(NO_3)_3.9H_2O$ 0.3 mmol, CH_3OH 5 mmol, THF 5 mL, reflux (70°C), 1 h

[a]$Cr(NO_3)_3.9H_2O$ 0.3 mmol, no THF

[b]$Cr(NO_3)_3.9H_2O$ 0.1 mmol, no THF

Table 3.6 presents the outcomes of the ring opening of cyclohexene oxide with CH_3OH under developed conditions. These data clearly showed that under the optimized conditions, the reactions mainly took place with the cleavage of epoxide to nitrate ester **5** (entry 1). The attempt to obtain the desired methoxyalcohol, *trans*-2-methoxycyclohexanol (**7**) was achieved by a bit modification as increasing the amount of CH_3OH whereas THF was not used as a solvent. CH_3OH could act as both solvent and nucleophile concomitantly.

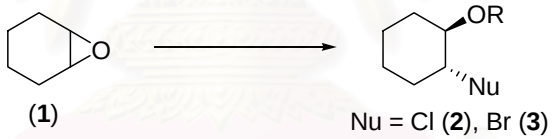
When CH_3OH was used as solvent replacing THF in the optimized condition, the desired product **7** was obtained in 78% (entry 2), however, still getting *trans*-2-nitratocyclohexanol (**5**) as a side product. The decrement of $Cr(NO_3)_3.9H_2O$ reagent might be needed in order to reduce this by-product. $Cr(NO_3)_3.9H_2O$ 0.1 mmol affected the reaction providing the increasing yield of desired product **7** while the side product **5** was decreased (entry 3). This attempt was successful when the amount of CH_3OH was increased to 10 mL. The quantitative yield of methoxyalcohol (**7**) was obtained (entry 4).

The ^{1}H-NMR spectrum of *trans*-2-methoxycyclohexanol (**7**) (Fig A11) displayed the signal belonging to the methoxy protons at δ_H 3.39 (3H, s). The hydroxy proton could be detected at δ_H 2.73 (1H, s). The protons adjacent to methoxy and hydroxyl groups were visualized at δ_H 2.90-2.96 (1H, ddd, J = 4.3, 8.7, 10.8 Hz) and 2.10-2.13 (1H, m), respectively. The methylene protons could be assigned at δ_H 1.98-2.01 (1H, m), 1.68-1.74 (3H, m) and 1.02-1.29 (4H, m).

It can thus be summarized that the conditions demonstrated above utilized a selective reagent for the ring opening of epoxide to alkoxyalcohol. This was probably a unique regioselectivity of this chromium-mediated reaction and made this reaction applicable for other nucleophile to synthesize a variety of useful compounds.

3.1.9 Comparative reactivity study of Cl^- and Br^- nucleophiles on the ring opening of cyclohexene oxide

The reactivity of halide ion on the ring opening of epoxide into halohydrin was competitively studied using $CrCl_3.6H_2O$ and $CrBr_3.6H_2O$. The results are presented in Table 3.7.



(**1**) Nu = Cl (**2**), Br (**3**)

Table 3.7 Comparative reactivity study of chromium halides on cyclohexene oxide ring opening

Entry	Reagent	%		MB
		recovered 1	2 or 3	
1	$CrCl_3.6H_2O$	-	**2** (97)	97
2	$CrBr_3.6H_2O$	-	**3** (100)	100
3	$CrCl_3.6H_2O$ +$CrBr_3.6H_2O$	-	**2** (11), **3** (93)	104

Reaction conditions: cyclohexene oxide 1 mmol, chromium reagent 1 mmol, THF 5 mL, room temperature, 30 min

From Table 3.7, the competitive study revealed that under these conditions either $CrCl_3.6H_2O$ or $CrBr_3.6H_2O$ gave the quantitative yield of the corresponding

halohydrin product (entries 1-2). However, when both $CrCl_3.6H_2O$ and $CrBr_3.6H_2O$ (1 mmol each) were added in the reaction, bromohydrin was detected as a major product (entry 3).

The competitive reactivity study of halide nucleophiles was also studied using LiX under the optimized condition. The results are revealed in Table 3.8.

Table 3.8 Comparative reactivity study of LiX on cyclohexene oxide ring opening

Entry	Additive	Time (min)	% recovered 1	% product	MB
1	LiCl	5	8	**2** (92)	100
2	LiBr	5	0	**3** (105)	105
3	LiCl+LiBr	3	3	**2** (6), **3** (92)	101

Reaction conditions: cyclohexene oxide 1 mmol, $Cr(NO_3)_3.9H_2O$ 0.3 mmol, additive 5 mmol, THF 5 mL, reflux (70°C)

Table 3.8 displays the result in the same trend as that obtained in Table 3.7. The condition used in this study was the same as that in optimized condition; however, shorten time was performed to study the reactivity of nucleophile. When the reaction time was 5 min, the addition of LiCl provided 92% yield of the desired chlorohydrin (entry 1), while LiBr gained quantitative yield of the corresponding product (entry 2). In addition, when both LiCl and LiBr (1 mmol each) were added, bromohydrin was emerged as a major product (entry 3). These results clearly indicated that bromide ion was superior in reactivity.

In accordance with previous observation [42, 37(b)], the reactivity of LiX definitely follows the order of LiI > LiBr >> LiCl. In the other words, the reactivity order of three halides was $I^- > Br^- > Cl^-$ coincident with many literatures [18, 48, 49].

3.1.10 Applications of developed ring opening reaction for other epoxides

The extended study on utilizing $Cr(NO_3)_3 \cdot 9H_2O$ in the ring opening of other epoxides was scrutinized under the optimized conditions. Various substrates included alkyl- and aryl-substituted epoxides were selected such as 1-dodecene oxide (**8**), *n*-butyl glycidyl ether (**9**), *tert*-butyl glycidyl ether (**10**), phenyl glycidyl ether (**11**), styrene oxide (**12**) and *trans*-stilbene oxide (**13**).

According to previous studies [48(b)], LiBr was the best choice among several metal bromides in the conversion of phenyl glycidyl ether to the corresponding bromohydrin. In addition, previous results showed the efficiency of LiBr additive that could complete the reaction under rapid and convenient condition. Therefore, LiBr was chosen as an additive in the reaction of $Cr(NO_3)_3 \cdot 9H_2O$ and all selected epoxides. The results are accumulated in Table 3.9.

Table 3.9 Ring opening of selected epoxides using $Cr(NO_3)_3.9H_2O$ and LiBr

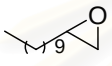
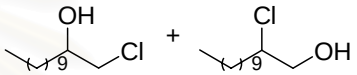
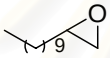
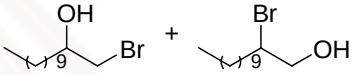
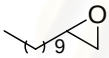
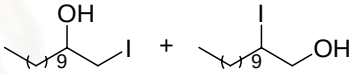
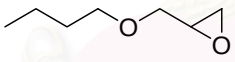
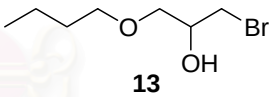
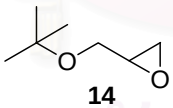
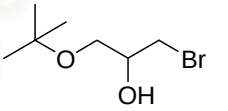
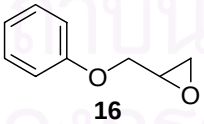
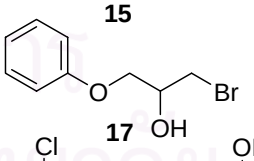
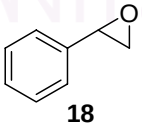
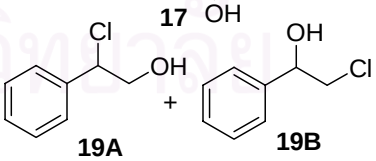
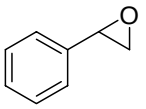
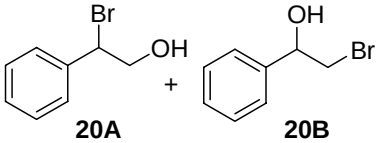
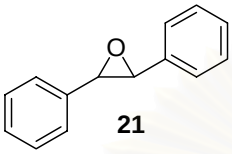
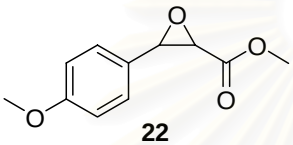
Entry	Substrate	Additive	% Isolated yield
1[a]	 **8**	LiCl	 **9A** + **9B** 99 (94:6)
2[a]		LiBr	 **10A** + **10B** 98 (95:5)
3[b]		LiI	 **11A** + **11B** quant (97:3)
4	 **12**	LiBr	 **13** quant
5	 **14**	LiBr	 **15** quant
6	 **16**	LiBr	 **17** 92
7[a]	 **18**	LiCl	 **19A** + **19B** 94 (77:23)

Table 3.9 (continued)

Entry	Substrate	Additive	% Isolated yield
8[a]		LiBr	 **20A** + **20B** 97 (98:2)
9[c]	 **21**	LiBr	-
10[c]	 **22**	LiBr	-

Reaction conditions: substrate 1 mmol, $Cr(NO_3)_3.9H_2O$ 0.3 mmol, additive 5 mmol, THF 5 mL, reflux, 5 min

[a]reaction time 1 h

[b]reaction time 30 min

[c]reaction time 5 h

Table 3.9 reveals that terminal alkyl and aryl epoxides could undergo ring opening with $Cr(NO_3)_3 \cdot 9H_2O$ under optimum conditions fruitfully and gave the desired products in good to quantitative yield with excellent selectivity. The use of LiBr 5 mmol could alter the reaction to produce bromohydrin in excellent yield under rapid condition (entries 2, 4-6, 8-9).

In the case of alkyl-substituted epoxides, a long-chain epoxide such as 1-dodecene oxide (entries 1-3) was chosen as a representative to explore the effect of type of external halides: LiCl, LiBr and LiI. This type of epoxide was relatively stable, not generally facile to be opened compared with other epoxides, thus suitable for studying the regioselectivity cleavage by $Cr(NO_3)_3 \cdot 9H_2O$. 1-Dodecene oxide (**8**) were converted to the corresponding halohydrins (1-chlorododecan-2-ol (**9A**), 1-bromododecan-2-ol (**10A**) and 1-iododododecan-2-ol (**11A**)) which derived from the attack of the halide ion on the less hindered side of the epoxide in high yield. These results were in accord with the propensity of Me_2BBr [50], TMSCl [51] and $CeCl_3$ [52] to cleave a C-O bond through an S_N2-type mechanism. All products were fully

characterized their identities by ^{1}H-NMR spectroscopy. Three products of 1-dodecene oxide ring opening namely 1-chlorododecan-2-ol (**9A**), 2-chlorododecan-1-ol (**9B**) and 1-bromododecan-2-ol (**10A**) were selected as examples.

The ^{1}H-NMR spectrum of 1-chlorododecan-2-ol (**9A**) (Fig A12) displayed the signal of the proton on the carbon next to a hydroxyl group at δ_H 3.80 (1H, br s). The protons adjacent to chlorine atom were visualized at δ_H 3.62-3.65 (1H, dd, J = 3.1, 11.0 Hz) and 3.45-3.50 (1H, dd, J = 7.2, 11.0 Hz), whereas the hydroxy proton could be detected at δ_H 2.14 (1H, s). The methylene protons of long chain carbons could be observed at δ_H 1.44-1.53 (2H, m) and 1.25 (16H, s). The triplet signal of methyl protons was found at δ_H 0.86-0.89 (3H, t, J = 6.6 Hz).

The ^{1}H-NMR spectrum of 2-chlorododecan-1-ol (**9B**) (Fig A13) visualized the signal of the proton on the carbon next to a hydroxyl group at δ_H 4.01-4.05 (1H, m). The protons adjacent to chlorine atom could be observed at δ_H 3.76-3.82 (1H, m) and 3.63-3.69 (1H, m), while the hydroxy proton could be detected at δ_H 2.00 (1H, s). The methylene protons of long chain carbons were observed at δ_H 1.68-1.77 (2H, m), 1.59 (1H, s), 1.51-1.54 (1H, m), 1.38-1.43 (1H, m) and 1.26 (13H, s). The triplet signal of methyl protons was found at δ_H 0.86-0.89 (3H, t, J = 6.3, 6.9 Hz).

The ^{1}H -NMR spectrum of 1-bromododecan-2-ol (**10A**) (Fig A14) displayed the signal of the proton on the carbon next to a hydroxyl group at δ_H 3.76 (1H, m). The proton adjacent to bromine atom was observed at δ_H 3.53-3.56 (1H, dd, J = 3.2, 10.3 Hz) and 3.36-3.40 (1H, dd, J = 7.1, 10.3 Hz), whereas the hydroxy proton could be detected at δ_H 2.24 (1H, s). The methylene protons of long chain carbons could be observed at δ_H 1.53 (2H, m) and 1.25 (16H, s). The triplet signal of methyl protons was also detected at δ_H 0.87 (3H, t, J = 6.5 Hz).

A more dramatic change was observed with glycidyl ether compounds such as butyl glycidyl ether, *tert*-butyl glycidyl ether and phenyl glycidyl ether (entries 4-6). It was found that these alkyl-substituted epoxides containing α-heteroatom underwent ring-opening to give the corresponding bromohydrins which bromide ion attacked on the less hindered side of the epoxide as the only compound detected in high to quantitative yield. The reaction of glycidyl ethers with bromide nucleophile afforded much higher selectivity than those with alkyl epoxides. This is presumably because glycidyl ethers can form a chelation with $Cr(NO_3)_3 \cdot 9H_2O$, which is more stable than the simple Cr-O formed by regular oxiranes, and are thus able to compete more effectively with the halide for the metal centre [53]. All obtained products such as

1-bromo-3-butoxypropan-2-ol (**13**), 1-bromo-3-*tert*-butoxypropan-2-ol (**15**) and 1-bromo-3-phenoxypropan-2-ol (**17**) were identified by ^{1}H-NMR spectroscopy.

The ^{1}H-NMR spectrum of 1-bromo-3-butoxypropan-2-ol (**13**) (Fig A15) visualized the signal of the proton on the carbon next to a hydroxy group at δ_H 3.93-3.98 (1H, quin, J = 5.3 Hz). The protons adjacent to ether group and bromine atom could be observed at δ_H 3.44-3.56 (6H, m), whereas the singlet signal of a hydroxy proton could be detected at δ_H 2.58-2.59 (1H, br s). The methylene protons could be assigned at δ_H 1.52-1.59 (2H, quin, J = 6.7 Hz) and 1.32-1.41 (2H, six, J = 7.4 Hz). The triplet signal of methyl protons were observed at δ_H 0.90-0.94 (1H, t, J = 7.37).

The ^{1}H-NMR spectrum of 1-bromo-3-*tert*-butoxypropan-2-ol (**15**) (Fig A16) visualized the signal of the proton on the carbon next to a hydroxy group at δ_H 3.91-3.87 (1H, m). The protons adjacent to ether group and bromine atom could be observed at 3.43-3.54 (4H, m), whereas the singlet signal of a hydroxy proton could be detected at δ_H 2.65 (1H, br s). The singlet signal of methyl protons were observed at δ_H 1.20 (9H, s).

The ^{1}H-NMR spectrum of 1-bromo-3-phenoxypropan-2-ol (**17**) (Fig A17) displayed the aromatic protons at δ_H 7.26-7.32 (2H, t, J = 7.9 Hz), 6.97-7.01 (1H, t, J = 7.3 Hz) and 6.91-7.01 (2H, d, J = 8.3 Hz). The multiplet signal of proton on the carbon next to a hydroxy group was detected at δ_H 4.16-4.24 (1H, m), while two protons adjacent to an ether group were visualized at δ_H 4.06-4.14 (2H, m). The protons adjacent to bromine atom could be observed at δ_H 3.58-3.62 (1H, dd, J = 5.7, 10.4 Hz) and 3.65-2.69 (1H, dd, J = 5.2, 10.4 Hz). The singlet signal of a hydroxy proton at δ_H 2.60 (1H, s) was also observed.

In the case of aryl-substituted epoxides, for example styrene oxide (**18**) (entry 7-8), the mechanistic pathway of this ring opening was underwent to give a mixture of bromohydrins which bromide ion attacked on the benzylic position of the epoxide as the main constituent in high to quantitative yield. Styrene oxide (entries 7-8) underwent ring opening to 2-chloro- (**19A**) and 2-bromo-2-phenylethanol (**20A**) as major products. All products were fully characterized their identities by ^{1}H-NMR spectroscopy. Three halohydrins namely 2-chloro-2-phenylethanol (**19A**), 2-chloro-1-phenylethanol (**19B**) and 2-bromo-2-phenylethanols (**20A**) were selected as examples.

The ^{1}H-NMR spectrum of 2-chloro-2-phenylethanol (**19A**) (Fig A18) showed the aromatic protons at δ_H 7.30-7.42 (5H, m). The signal of benzylic proton adjacent to chlorine atom could be observed at δ_H 4.96-4.99 (1H, dd, J = 5.7, 7.4 Hz), while the

methylene protons next to a hydroxyl group could be assigned at δ_H 3.87-3.91 (1H, dd, J = 5.7, 12.0 Hz) and 3.90-3.95 (1H, dd, 7.4, 12.0 Hz). The singlet signal of a hydroxy proton at δ_H 2.82 (1H, s) was also observed.

The ^{1}H-NMR spectrum of 2-chloro-1-phenylethanol (**19B**) (Fig A19) showed the aromatic protons at δ_H 7.38-7.39 (5H, d, *J* = 4.4 Hz). The signal of benzylic proton adjacent to a hydroxyl group could be observed at δ_H 4.88-4.90 (1H, dd, *J* = 3.5, 8.8 Hz), while the methylene protons next to chlorine atom could be assigned at δ_H 3.71-3.75 (1H, dd, *J* = 3.5, 11.2 Hz) and 3.62-3.67 (1H, dd, *J* = 8.8, 11.2 Hz). The singlet signal of a hydroxy proton at δ_H 2.89 (1H, s) was detected.

The ^{1}H-NMR spectrum of 2-bromo-2-phenylethanol (**20A**) (Fig A20) showed the aromatic protons at δ_H 7.30-7.38 (5H, d, *J* = 3.9 Hz). The triplet signal of benzylic proton adjacent to a hydroxyl group could be observed at δ_H 4.88-4.91 (1H, dd, *J* = 3.6, 8.7 Hz), whereas the methylene protons next to bromine atom could be assigned at δ_H 3.60-3.63 (1H, dd, *J* = 3.6, 10.5 Hz) and 3.51-3.55 (1H, dd, *J* = 8.8, 10.5 Hz). The singlet signal of a hydroxy proton at δ_H 3.14 (1H, s) was visualized.

To observe the effect of the substituent at β-position of aryl-substituted epoxides, *trans*-stilbene oxide (**21**) and methyl *trans*-3-(4-methoxyphenyl)-glycidate (**22**) were investigated (entries 9-10).

For *trans*-stilbene oxide (**21**), the effect of π-orbital of phenyl group and the substituent at β-position was not influent the reaction although the reaction time was increasing to 5 h (entry 9). The same result was obtained when methyl *trans*-3-(4-methoxyphenyl)-glycidate (**16**), which bearing an electron-withdrawing group, was used as the reactant (entry 10). The reasons to explain this observation were that the steric hinder of epoxide ring played important role in the coordination of chromium reagent and the oxygen of epoxide. The hindered epoxide such as disubstituted epoxides was shielded by the substituent, therefore, chromium could not coordinate with lone pair electron of the oxygen of epoxide. From this reason, the ring opening was not occurred.

Part II : Transformation of cyclohexene oxide to aminoalcohol

To verify the identity of the desired aminoalcohol product, ^{1}H-NMR spectroscopy was utilized. The ^{1}H-NMR spectrum of *trans*-2-(phenylamino) cyclohexanol (**23**) (Fig 3.5) revealed the aromatic protons at δ_H 7.16-7.20 (2H, t, J = 7.8 Hz) and 6.71-6.77 (3H, dd, J = 7.6, 15.5 Hz). The α-proton could be assigned at δ_H 3.33-3.38 (1H, td, J = 4.2, 9.7 Hz), whereas that at carbon connecting with nitrogen atom could be visualized at δ_H 3.12-3.18 (1H, ddd, J = 3.8, 9.2, 10.9 Hz). The singlet signal of a hydroxy proton was observed at δ_H 2.40 (1H, br s). The methylene protons could be assigned at δ_H 2.11-2.14 (2H, m), 1.71-1.79 (2H, m), 1.29-1.42 (3H, m) and 1.00-1.11 (1H, m). The ^{13}C-NMR spectrum (Fig 3.6) displayed six aromatic carbons at δ_C 147.9, 129.3 (2C), 118.1 and 114.3 (2C). The methylene carbon adjacent to a hydroxy group was detected at δ_C 74.4, The peak at δ_C 60.0 indicated the carbons adjacent to nitrogen atom. The other peaks at δ_C 33.4, 31.6, 25.0 and 24.3 indicated the methylene carbons.

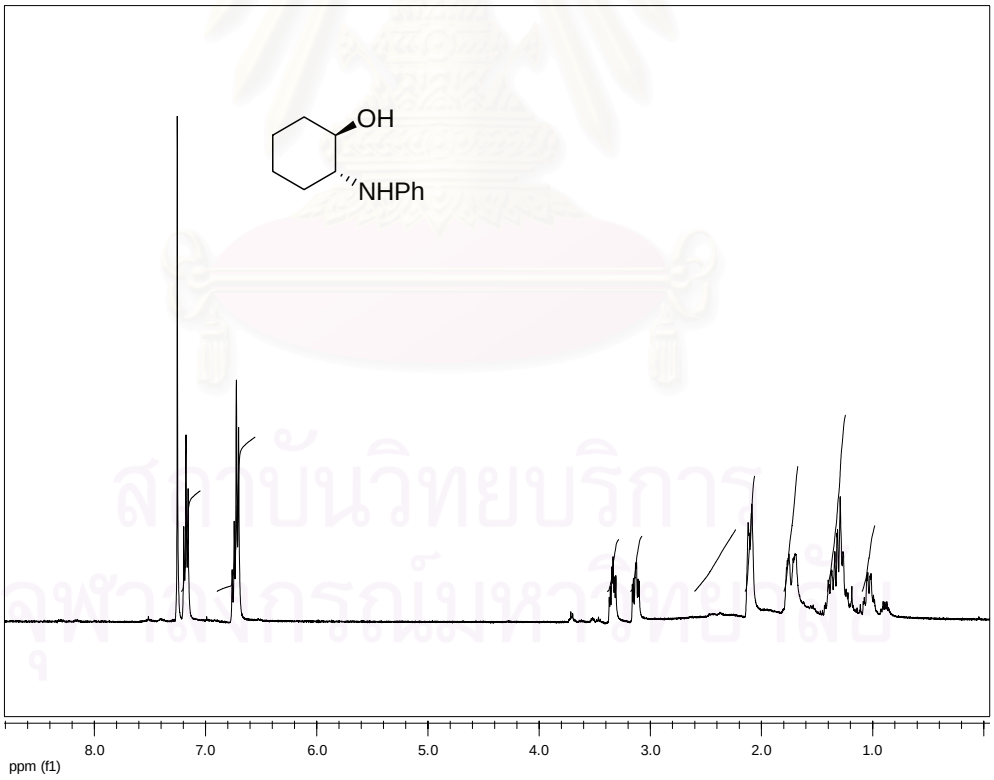


Figure 3.5 The ^{1}H-NMR spectrum of *trans*-2-(phenylamino)cyclohexanol (**23**)

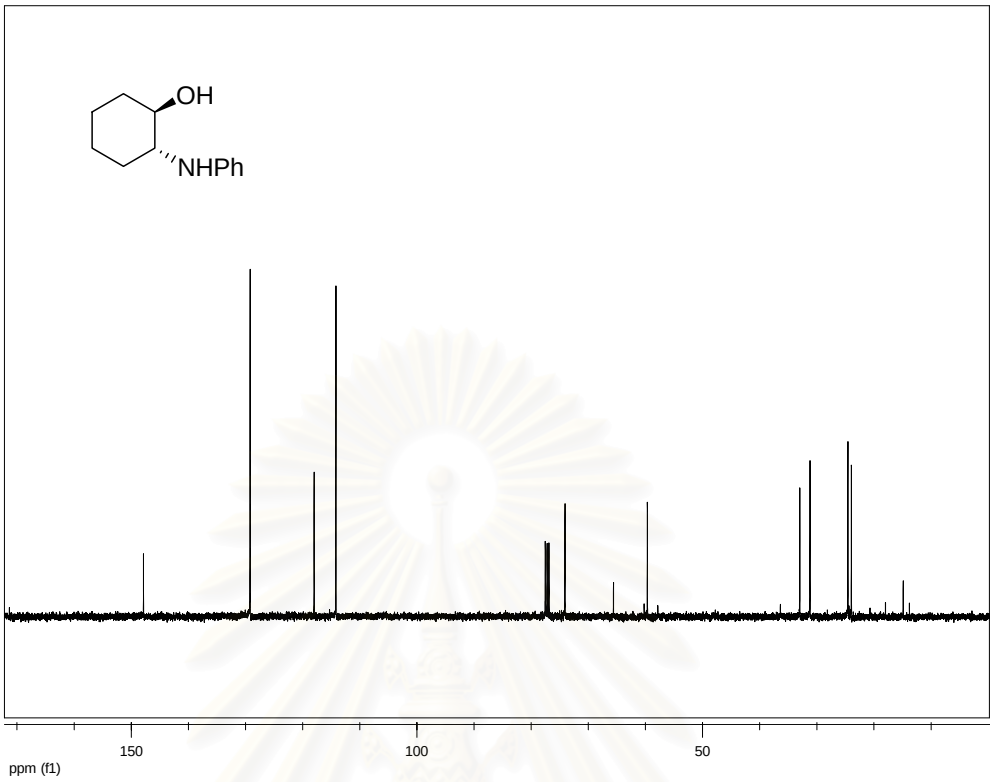


Figure 3.6 The ^{13}C-NMR spectrum of *trans*-2-(phenylamino)cyclohexanol (**23**)

3.1.11 Effect of solvent on cyclohexene oxide ring opening to aminoalcohol by $CrCl_3.6H_2O$ with aniline

As part of the aim towards the new synthetic methodology of aminoalcohol, the ring opening of epoxide with amine utilizing $CrCl_3.6H_2O$ was investigated. At first, to define the conditions for aminolysis of cyclohexene oxide with amine, suitable solvents should be examined. From the result in Part I, the compatibility of solvent and $CrCl_3.6H_2O$ played important role. The attempt to search for appropriate solvent that could mediate the formation of aminoalcohol product in high yield with good selectivity was also studied.

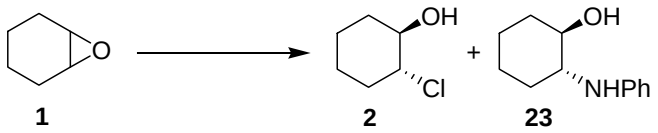
According to previous studies [29], cyclohexane was the best choice among several solvents in the conversion of epoxide to the corresponding aminoalcohol in moderate to high yield. Therefore, in this study cyclohexane was first chosen as a solvent in the reaction of $CrCl_3.6H_2O$ and cyclohexene oxide in the presence of aniline. In addition, the previous study [29] revealed the general condition for aminoalcohol synthesis as: epoxide 1 mmol, amine 1.1 mmol, solvent 0.5 mL and $BiCl_3$ 0.1 mmol at 20ºC for 7-11 h.

From the optimized conditions for halohydrin synthesis in Part I, the condition was a bit modified to obtain the suitable conditions for this purpose. The selected condition consisted of epoxide 1 mmol, amine 1.1 mmol, solvent 5 mL and $CrCl_3.6H_2O$ 0.1 mmol at reflux for 6 h. Under this particular condition, the ring opening of cyclohexene oxide (**1**) provided *trans*-2-(phenylamino)cyclohexanol (**23**) as a major product. The effects of type of selected solvents, such as THF and cyclohexane, on cyclohexene oxide ring opening are consequently examined.

Gaining the information from the experimental results, cyclohexane displayed low efficiency towards the transformation giving aminoalcohol in 39%, compared with THF 51%. In addition, chlorohydrin by-product was also obtained from the result of $CrCl_3.6H_2O$ in 25% and 27% using cyclohexane and THF, respectively. From this study, THF still appeared to be more suitable solvent than cyclohexane to furnish the higher yield of aminoalcohol. The result could be explained by the homogeneity of $CrCl_3.6H_2O$ in the solvent as in Part I.

3.1.12 Effect of the amount of substrate, aniline and $CrCl_3.6H_2O$ on epoxide ring opening to aminoalcohol

In order to find the optimized conditions to provide aminoalcohol, the variation on the reaction parameters was studied. The results are summarized as shown in Table 3.10.



1 2 23

Table 3.10 Effect of the amount of substrate, aniline and $CrCl_3.6H_2O$

Entry	Substrate (mmol)	$PhNH_2$ (mmol)	$CrCl_3 \cdot 6H_2O$	%		MB
				recovered 1	product	
1	1.0	1.1	0.1	21	**2** (27), **23** (51)	99
2	0.5	1.1	0.1	6	**2** (46), **23** (50)	101
3	1.0	3.0	0.1	7	**2** (19), **23** (71)	97
4	1.0	5.0	0.1	0	**2** (19), **23** (80)	99
5	1.0	5.0	0.05	5	**2** (12), **23** (87)	104
6	1.0	10.0	0.1	0	**2** (16), **23** (84)	100

Reaction conditions: THF 5 mL, reflux, 6 h

With the aim to find the suitable amount of substrate, the amount of cyclohexene oxide was decreased to 0.5 mmol. The result demonstrated the increasing ratio of substrate per the amount of $CrCl_3.6H_2O$ was not affected on the increasing yield of desired product, aminoalcohol (**23**), but the yield of undesirable halohydrin by-product (**2**) was increased to moderate yield (entry 2).

The quantity of nucleophile was also studied to affect the reaction. The amount of aniline in the reaction was varied from 1.1 to 10 mmol. When 5.0 mmol of aniline was employed, the reaction afforded the highest yield of aminoalcohol (entry 3). When the amount of aniline was increased or decreased from 5.0 mmol, the yield of aminoalcohol were declined. Using of 1.1 and 3.0 mmol of aniline, the lower yield of product compared to the use of 5.0 mmol of aniline was obtained and the transformation was not completed (entries 1 and 3). The more amount of aniline than 5.0 mmol did not have any significant effect to increase the yield (entry 6).

With the aim to reduce halohydrin by-product, which derived from $CrCl_3.6H_2O$, the decreasing on the amount of this catalyst to 0.05 mmol was studied. The result showed indifferent of the yield. It was disclosed that 0.1 mmol of $CrCl_3.6H_2O$ was still appeared to be the optimal amount of catalyst (entry 2). This result indicated that the use of lower amounts of catalyst led to lower efficiency to complete the reaction.

3.1.13 Kinetic study on cyclohexene oxide ring opening by $CrCl_3.6H_2O$ with aniline

This study examined the appropriate time for the ring opening of cylohexene oxide with aniline. The results are presented in Fig 3.7.

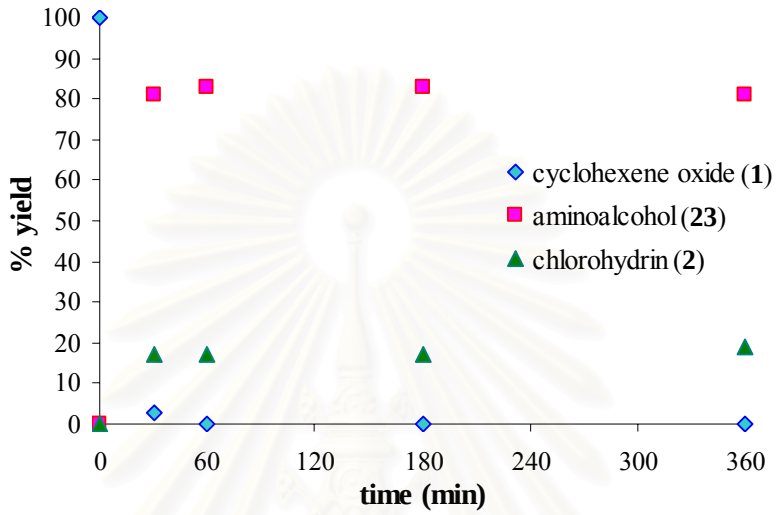


Figure 3.7 Kinetic study on the ring opening of cyclohexene oxide (**1**) to aminoalcohol (**23**) with aniline by $CrCl_3.6H_2O$

From the results depicted in Fig 3.7, after 30 min, cylohexene oxide was decreased dramatically while *trans*-2-(phenylamino)cyclohexanol (**23**) was gradually occurred. The reaction was completed and yielded **23** after 1 h (81%). The formation of halohydrin by-product, *trans*-2-chlorocyclohexanol (**2**), was simultaneously obtained when the reaction proceeded. This study showed that the suitable reaction time was 1 h. The prolonged reaction time did not have any effect to increase the yield of aminoalcohol.

3.1.14 Kinetic study on cyclohexene oxide ring opening by $Cr(NO_3)_3.9H_2O$ with aniline

In order to avoid halohydrin by-product which derived from $CrCl_3.6H_2O$, $Cr(NO_3)_3.9H_2O$ was chosen. The kinetic study on the ring opening of cyclohexene oxide was also investigated and the results are shown in Fig 3.8.

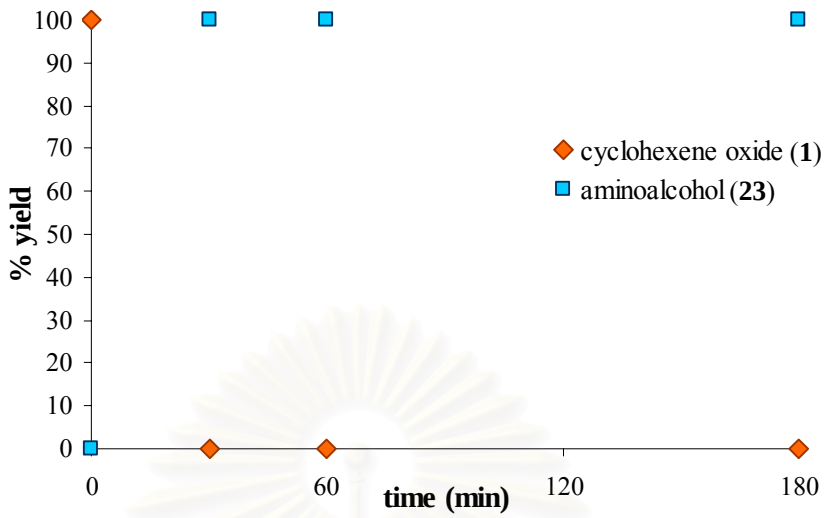
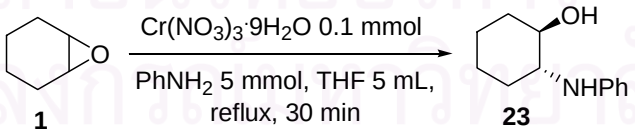


Figure 3.8 Kinetic study on the ring opening of cyclohexene oxide (**1**) to aminoalcohol (**23**) with aniline by $Cr(NO_3)_3.9H_2O$

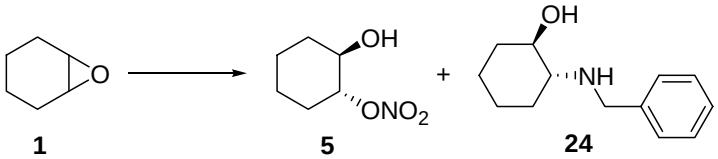
From the experimental result presented in Fig 3.8, after 30 min, cylohexene oxide was completely transformed to *trans*-2-(phenylamino)cyclohexanol (**23**). The quantitative yield of **23** was attained without any by-product formed. The good selectivity was obtained when $Cr(NO_3)_3.9H_2O$ was used as catalyst.

From the above results, it could be summarized that the optimum conditions for the selective transformation of cyclohexene oxide into aminoalcohol are as follows: cyclohexene oxide 1 mmol as a substrate, $Cr(NO_3)_3.9H_2O$ 0.1 mmol as a catalyst, aniline 5 mmol as nucleophile in a solvent THF 5 mL at reflux for 30 min. The quantitative yield of the corresponding *trans*-2-(phenylamino)cyclohexanol (**23**) was obtained.



3.1.15 Effect of time, the amount of $Cr(NO_3)_3.9H_2O$ and aniline on cyclohexene oxide ring opening with benzylamine

The application of the optimized conditions was applied with other nucleophiles. Benzylamine was chosen as the representative nucleophile with the effect of benzyl position. The results are presented in Table 3.11.



1 5 24

Table 3.11 Effect of time, the amount of $Cr(NO_3)_3.9H_2O$ and aniline on cyclohexene oxide (**1**) ring opening with benzylamine

Entry	$Cr(NO_3)_3.9H_2O$ (mmol)	$PhCH_2NH_2$ (mmol)	Time	% recovered 1	% product	MB
1	0.1	5	30 min	100	-	100
2	0.1	5	7 day	-	**24** (105)	105
3	0.1	5	24 h	100	-	100
4[a]	0.3	5	24 h	41	**5** (3), **24** (51)	98
5[a]	0.5	5	24 h	2	**5** (4), **24** (90)	98
6[a]	0.5	1.1	24 h	3	**5** (3), **24** (1)	74
7[a]	0.5	3	24 h	81	**5** (4), **24** (14)	99
8[a]	1.0	5	24 h	19	**5** (11), **24** (61)	95

Reaction conditions: cyclohexene oxide 1 mmol, THF 5 mL, $PhCH_2NH_2$ 5 mmol, reflux

[a]Mass balance included unidentified products

From the results presented in Table 3.11, the reaction was not occurred under the optimized condition for aniline nucleophile (entry 1). Even the reaction time was increased to 24 h, the reaction still not took place and the substrate was 100% recovered (entry 3). Nevertheless, if the reaction time was prolonged to 7 days, the aminoalcohol (**24**) accordingly obtained in quantitative yield (entry 2). This long reaction time was made this condition not practically.

The attempt to search for more suitable and rapid reaction was explored. The dependence on the amount of $Cr(NO_3)_3.9H_2O$ was directly influenced the outcome of the transformation of cyclohexene oxide. When $Cr(NO_3)_3.9H_2O$ was increased to 0.3 and 0.5 mmol, the yield of the desired product was consequently increased (entries 4-5). However, when $Cr(NO_3)_3.9H_2O$ was increased to 1 mmol, the reaction did not provide the rising yield of product (entry 8). It was seemed that the aminoalcohol was obtained in the highest yield when 0.5 mmol of $Cr(NO_3)_3.9H_2O$ was used (entry 5).

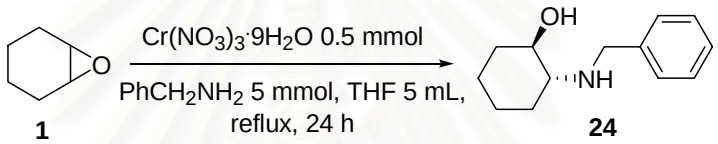
Concerning the reactivity, it may explain by the quantity of the amines used. The effect on the amount of amine was studied in order to decrease the amount of an excess amine. Since it could be observed that when 1.1 mmol of benzylamine was allowed to react with cyclohexene oxide in THF (entry 6), the reaction was not selective gaining very poor yield of the desired product even after 1 day at reflux. Even the amount of benzylamine 3 mmol was used, the reaction was still not reactive giving only low yield and the substrate was recovered in 81% (entry 7). Applying an excess of benzylamine in 5 mmol still seemed to be the best improvement, whereby a good yield of 90% was obtained. The same improvement in yield upon increasing the amounts of the benzylamine used was also applicable for other amines. This was in agreement with Das [54], who reported that the method using hexafluoro-2-propanol (HFIP) failed to promote cyclohexene oxide ring opening with both diethylamine and benzylamine at 1.1 equiv under reflux for 4 days.

The reaction rate of aminoalcohol synthesis using benzylamine as nucleophile was slower than that of aniline. It might be, therefore, explained by the basicity of amines which contributed to their reactivity. For aniline, aromatic nucleophile, partially or fully delocalization of lone pair electron at nitrogen atom into π-electron of aromatic ring was able to withdraw electron density. Therefore, the basicity of aniline was lower than benzylamine which had no effect of the delocalization of lone pair of electron at nitrogen atom. Thus, the stronger base benzylamine was more favor to react and formed stronger bond with chromium Lewis acid than aniline affecting the decreasing on the reactivity to react with the epoxide. The complexation between amine and chromium reagent could observe from the precipitate formed in the solution. Similar behaviors were reported with $CoCl_2$ [30], $TaCl_5$ [55], $CeCl_3$ [56] and metal triflates systems [7(h), 57].

The ^{1}H-NMR spectrum of *trans*-2-(benzylamino)cyclohexanol (**24**) (Fig A21) revealed the aromatic protons at δ_H 7.30-7.33 (4H, m) and 7.23-7.27 (1H, m). The benzylic proton connecting with nitrogen could be detected at δ_H 3.93-3.97 (1H, d, J = 12.9 Hz) and 3.67-3.71 (1H, d, J = 12.9 Hz). The α-protons could be assigned at δ_H 3.18-3.24 (1H, td, J = 4.7, 9.7 Hz), whereas those at carbon connecting with nitrogen atom in a cyclic ring could be visualized at δ_H 2.27-2.33 (1H, ddd, J = 3.9, 9.4, 11.2 Hz). The singlet signal of a hydroxy proton was observed at δ_H 2.45 (1H, br s). The methylene protons could be assigned at δ_H 2.14-2.17 (1H, m), 1.99-2.04 (1H, m),

1.71-1.74 (2H, m), 1.20-1.30 (3H, m) and 0.95-1.05 (1H, m). The ^{13}C-NMR spectrum (Fig A22) displayed six aromatic carbons at δ_C 140.4, 128.4 (2C), 128.1 (2C) and 127.0. The methylene carbon adjacent to a hydroxy group was detected at δ_C 73.7. The peak at δ_C 63.1 and 50.7 indicated the carbons adjacent to nitrogen atom in a cyclic ring and benzylic position, respectively. The other peaks at δ_C 33.3, 30.5, 25.1 and 24.3 indicated methylene carbons.

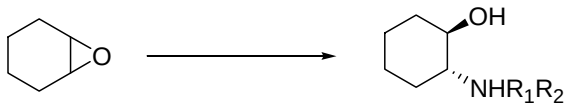
The optimum conditions for the selective transformation of cyclohexene oxide to aminoalcohol using benzylamine as a nucleophile are as follows: cyclohexene oxide 1 mmol as a substrate, $Cr(NO_3)_3.9H_2O$ 0.5 mmol as a catalyst, nucleophile benzylamine 5 mmol and THF 5 mL as a solvent at reflux for 24 h. The high yield of the corresponding *trans*-2-(benzylamino)cyclohexanol (**24**) was obtained.



1 **24**

3.1.16 Effect of various amines on cyclohexene oxide ring opening using $Cr(NO_3)_3.9H_2O$

In order to determine the role that steric and electronic effects would play in these reactions, a variety of aryl- and alkylamines were used to react with the epoxide. The amines used can be classified into 3 types: (i) aliphatic primary amines, (ii) aliphatic secondary amines and (iii) aromatic amines. The ring opening of cyclohexene oxide with various amines such as cyclohexylamine, piperidine, diethylamine, *N*-methylaniline, *p*-chloroaniline, *p*-nitroaniline, naphthylamine and 4-chloro-3-nitroaniline was studied. The results are shown in Table 3.12.



1

Table 3.12 Effect of various amines on cyclohexene oxide (**1**) ring opening

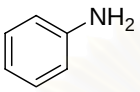
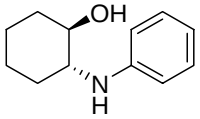
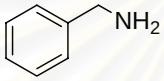
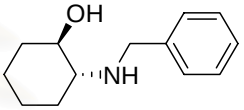
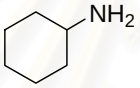
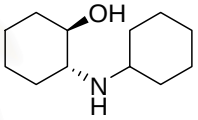
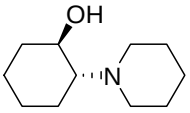
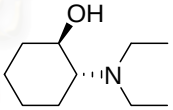
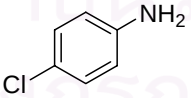
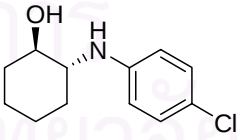
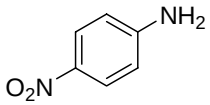
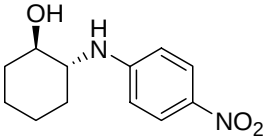
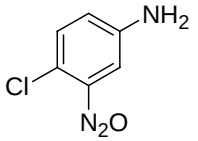
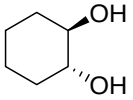
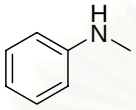
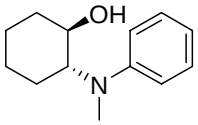
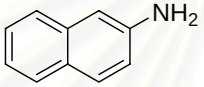
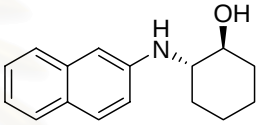
Entry	RNH_2	% Isolated yield
1		 **23** (96)[a]
2		 **24** (90)[a]
3		 **25** (90)
4		 **26** (quant)
5		 **27** (57)
6		 **28** (67)
7		 **29** (trace)

Table 3.12 (continued)

Entry	RNH_2	% Isolated yield
8		 **30** (50)
9		 **31** (34)
10		 **32** (42)

Reaction conditions: cyclohexene oxide 1 mmol, THF 5 mL, catalyst 0.5 mmol, amine 5 mmol, reflux, 24 h

[a]GC yield

The reactivity of cyclohexene oxide ring opening with amines was highly dependent on the basicity of amine relative to the acidity of Lewis acid, $Cr(NO_3)_3 \cdot 9H_2O$. In general, alkylamines are harder bases than aromatic amines because alkylamines did not have the effect from the delocalization of lone pair of electron at nitrogen atom. This was in line with the "hard-soft acid-base" theory proposed by Pearson [58] which classified alkylamines as hard bases while arylamines as borderline bases. Therefore, alkylamines were more efficiently to coordinate with catalyst. From the results in Table 3.12, primary and secondary aliphatic amines (entries 2-5) were reactive to epoxide providing the corresponding desired product in high yield excepted in diethylamine case. Longer reaction time or higher amount of $Cr(NO_3)_3 \cdot 9H_2O$ might be required for diethylamine than those for other aliphatic amines. Because of diminished reactivity probably arose due to a combination of the steric effects and catalyst deactivation. All products were fully characterized their identities by ^{1}H-NMR spectroscopy. The aminoalcohols namely *trans*-2-(cyclohexylamino) cyclohexanol (**25**) and *trans*-2-(piperidino)cyclohexanol (**26**) were selected as examples.

The ^{1}H-NMR spectrum of *trans*-2-(cyclohexylamino)cyclohexanol (**25**) (Fig A23) revealed the α-protons at δ_H 3.06-3.12 (1H, td, J = 4.7, 9.7 Hz), whereas those at β-carbon connecting with nitrogen could be visualized at δ_H 2.25-2.31 (1H, ddd, J = 3.8, 9.4, 11.2 Hz). The singlet signal of a hydroxy proton was observed at δ_H 2.41 (1H, br s). The proton at carbon in cyclohexyl group connecting with nitrogen could be assigned at δ_H 2.54-2.61 (1H, tt, J = 3.6, 10.2 Hz). The methylene protons in a cyclic ring could be assigned at δ_H 2.03-2.06 (2H, m), 1.89-1.92 (1H, m), 1.70-1.73 (1H, m), 1.57-1.60 (1H, m) and 1.10-1.33 (3H, m). The methylene protons in cyclohexyl group was observed at δ_H 1.70-1.73 (4H, m), 1.10-1.33 (4H, m) and 0.89-1.04 (2H, m).

The ^{1}H-NMR spectrum of *trans*-2-(piperidino)cyclohexanol (**26**) (Fig. A24) revealed the α-protons at δ_H 3.94 (1H, s), whereas those at β-carbon connecting with nitrogen could be visualized at δ_H 3.23-3.28 (1H, m). The proton at carbon in piperidyl group connecting with nitrogen could be assigned at δ_H 2.56-2.60 (2H, m) and 2.21-2.26 (2H, m). The methylene protons in a cyclic ring could be observed at δ_H 2.02-2.07 (2H, m), 1.68-1.71 (2H, m), 1.60-1.61 (1H, m) and 1.00-1.20 (5H, m). The methylene protons in piperidyl group were detected at δ_H 1.45-1.53 (4H, m) and 1.35-1.36 (2H, m).

In case of aromatic amines with electron withdrawing group (entries 6-9), the aminoalcohol product was obtained in low yield. It might be explained by the basicity of amine which contributed to their reactivity of the reaction. For aromatic amines, partially or fully delocalization of lone pair of electron at nitrogen atom into π-electron of aromatic ring was also able to withdraw electron density on nitrogen atom, especially, in the case of *p*-chloroaniline (entry 6) and *p*-nitroaniline (entry 7) which had the effect from electron withdrawing group. Thus, the basicity of these amines was too low to assist the reaction resulting in low yield of product. The same result was observed in the case of 4-chloro-3-nitroaniline (entry 8), which had strongly effect of two electron withdrawing groups: chloro and nitro groups, the corresponding aminoalcohol was not obtained, instead a diol compound (**30**) was detected in moderate yield. This diol by-product also observed in the case of using $CeCl_3.7H_2O$ [53(c)]. For *N*-methylaniline (entry 9), there was no effect derived from the electron withdrawing group; however, the low yield was obtained possibly from the effect of steric. From this reason, *N*-methylaniline might be hard to react with the chromium

reagent to form aminoalcohol. Therefore, the product was obtained in low yield. For naphthylamine (entry 10), which had the effect of the delocalization of electron into an aromatic ring, the product was obtained in moderate yield. All products were characterized their identities by ^{1}H-NMR spectroscopy. The aminoalcohols: *trans*-(4-chloroanilino)cyclohexanol (**28**), *trans*-(naphthylamino) cyclohexanol (**32**) and the diol, *trans*-1,2-cyclohexandiol (**30**), were selected as examples.

The ^{1}H-NMR spectrum of *trans*-(4-chloroanilino)cyclohexanol (**28**) (Fig A25) revealed the aromatic protons at δ_H 7.10-7.12 (2H, d, J = 7.8 Hz) and 6.62-6.64 (2H, d, J = 7.8 Hz). The α-protons could be assigned at δ_H 3.32-3.38 (1H, td, J = 4.0, 9.5 Hz), whereas those at the carbon connecting with nitrogen atom in a cyclic ring could be visualized at δ_H 2.98-3.11 (1H, td, J = 3.7, 10.0 Hz). The singlet signal of a hydroxy proton was observed at δ_H 2.59 (1H, br s). The methylene protons could be assigned at δ_H 2.07-2.13 (2H, m), 1.71-1.73 (2H, m), 1.24-1.43 (3H, m) and 1.00-1.11 (1H, m).

The ^{1}H-NMR spectrum of *trans*-(naphthylamino)cyclohexanol (**32**) (Fig A25) revealed the aromatic protons at δ_H 7.81-7.87 (2H, m), 7.46-7.48 (2H, m), 7.26-7.38 (2H, m) and 6.77-6.83 (1H, m). The α-protons could be assigned at δ_H 3.52-3.58 (1H, td, J = 4.2, 9.7 Hz), whereas those at the carbon connecting with nitrogen atom in a cyclic ring could be visualized at δ_H 3.35-3.40 (1H, td, J = 3.7, 10.3 Hz). The methylene protons could be assigned at δ_H 2.24-2.27 (1H, d, J = 13.1 Hz), 2.16-2.19 (1H, d, J = 13.1 Hz), 1.74-1.82 (2H, m), 1.32-1.49 (3H, m) and 1.09-1.17 (1H, m).

The ^{1}H-NMR spectrum of *trans*-1,2-cyclohexanediol (**30**) (Fig A26) revealed the hydroxy proton at δ_H 2.74 (1H, br s). The α-protons could be assigned at δ_H 3.66-3.72 (1H, m), whereas those at carbon connecting with chloride could be visualized at δ_H 3.47-3.50 (1H, m).

3.1.17 The ring opening of other epoxides by aniline with $Cr(NO_3)_3.9H_2O$

A regioselectivity in ring opening of three selected epoxides with amine was investigated. Aminolysis of selected epoxide including styrene oxide, cyclohexene oxide and 1-dodecene oxide, the representative of aromatic and aliphatic epoxides respectively, with aniline was compared. The results are shown as in Table 3.13.

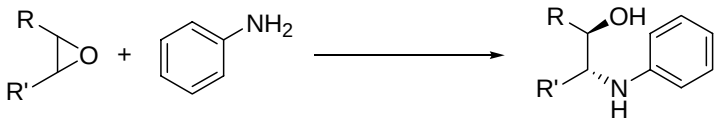
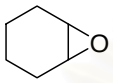
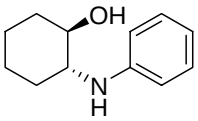
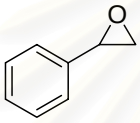
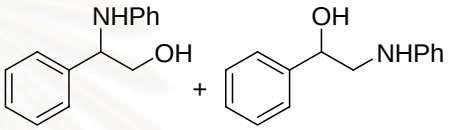
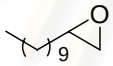
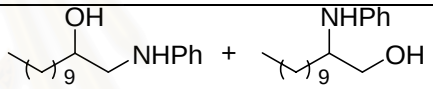


Table 3.13 The ring opening of epoxides by aniline using $Cr(NO_3)_3.9H_2O$

Entry	Epoxide	% Product
1		 99
2		 **33A** **33B** 98% (95:5)[a]
3		 **34A** **34B** quant (84:16)[a]

Reaction conditions: cyclohexene oxide 1 mmol, THF 5 mL, catalyst 0.1 mmol, $PhNH_2$ 5 mmol, reflux, 6 h

[a]The ratio was determined by GC

From the result in Table 3.13, in the case of styrene oxide as a substrate (entry 2), the preference for the formation of the aminoalcohol derived from the attack at the benzylic carbon (α-product) may be explained by the effect of Lewis acidic metal ion or low pH required to activate the oxirane ring. This allowed the transition state constituting a partial positive charge at the benzylic carbon stabilized by delocalization energy of benzene ring. The preference of obtaining the α-product was observed.

In the case of alkyl-substituted epoxides, 1-dodecene oxide could be converted to the corresponding aminoalcohol derived from the attack of the amine on the terminal carbon of the epoxide as the major product (entry 3). This cleavage demonstrated the regioselective going through an S_N2 mechanism which underwent

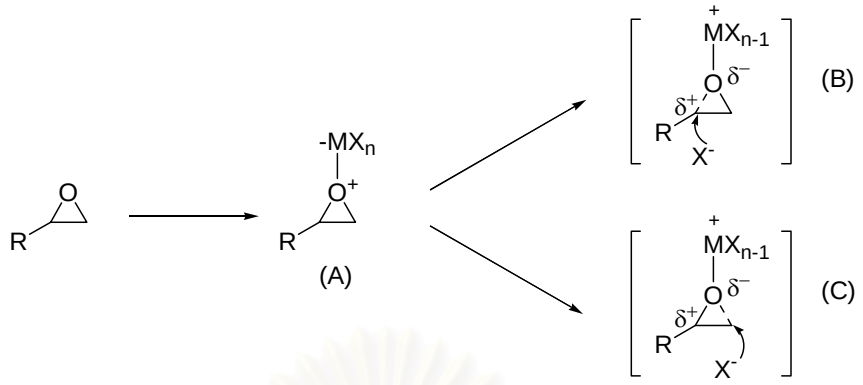
the nucleophilic attack on less hindered side of epoxide. All products were characterized their identities by ^{1}H-NMR spectroscopy. The aminoalcohols, namely 2-anilino-2-phenyl-1-ethanol (**33A**) and 2-anilino-2-dodecanol (**34A**) were selected as examples.

The ^{1}H-NMR spectrum of 2-anilino-2-phenyl-1-ethanol (**33A**) (Fig A27) revealed the aromatic protons connecting with β-carbon at δ_H 7.18-7.30 (5H, m), whereas those at the carbon connecting with nitrogen atom at δ_H 7.01-7.05 (2H, t, J = 7.8 Hz), 6.59-6.62 (1H, t, J = 7.3 Hz) and 6.49-6.51 (2H, d, J = 7.85 Hz). The protons at the carbon connecting to a hydroxyl group could be assigned at δ_H 4.42-4.44 (1H, dd, J = 4.2, 6.8 Hz) and 3.85-3.88 (1H, dd, J = 4.2, 11.1 Hz). The proton at the carbon connecting with nitrogen atom could be visualized at δ_H 3.66-3.70 (1H, dd, J = 6.9, 11.1 Hz). The hydroxy proton could be detected at δ_H 2.09 (1H, s).

The ^{1}H-NMR spectrum of 2-anilino-2-dodecanol (**34A**) (Fig A28) revealed the aromatic protons at δ_H 7.17-7.20 (2H, dd, J = 7.5, 8.4 Hz), 6.72-6.75 (1H, t, J = 7.3 Hz) and 6.65-6.67 (2H, d, J = 7.7 Hz). The signal of the proton on the carbon next to a hydroxyl group at δ_H 3.80-3.86 (1H, m). The proton adjacent to nitrogen atom was observed at δ_H 3.25-3.29 (1H, dd, J = 3.1, 12.9 Hz), 2.97-3.03 (1H, dd, J = 8.6, 12.9 Hz), whereas the hydroxy proton and the proton on nitrogen atom could be detected at δ_H 2.02 (2H, br s). The methylene protons of long chain carbons could be observed at δ_H 1.51-1.56 (2H, m), 1.26 (16H, br s). The triplet signal of methyl protons was also detected at δ_H 0.86-0.90 (3H, t, J = 6.7 Hz).

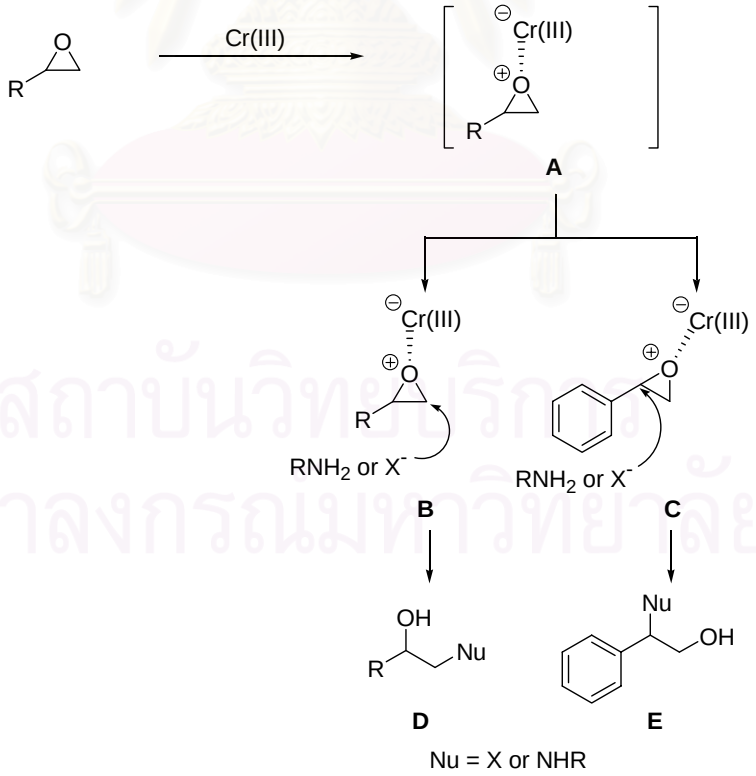
3.2 Proposed mechanism for epoxide ring opening to halohydrin and aminoalcohol

In principle, these reactions are well-explained by taking an account of mechanism based on the regiochemical modes of cleaving epoxides by metal halides. This could be viewed as occurring *via* two pathways, either electrophilic attack by MX_n, giving the more stable carbenium ion like transition state B or nucleophilic attack by halide ion on the epoxide-metal halide complex A, giving the more stable transition state C. These mechanistic extremes closely resemble S_N1 and S_N2 models for aliphatic nucleophilic displacement (Scheme 3.1) [21, 37(a), 59]. The ring opening of epoxides with halides or alkyl/aryl amine would lead to halohydrin or aminoalchol, respectively.



Scheme 3.1 Proposed mechanistic pathway for the ring opening of epoxides to halohydrin and aminoalcohol [21, 37(a)]

Taking into the consideration on the mechanistic pathway described above as well as the mechanism previously determined for related epoxide halogenative cleavage to halohydrin [18-23, 35-44, 48-52, 59] and aminolysis to aminoalcohol [27-33, 54-58], the reaction of cyclohexene oxide (**1**) by $CrCl_3.6H_2O$ or $Cr(NO_3)_3.9H_2O$ could proceed by the mechanistic scenario depicted in Scheme 3.2.



Scheme 3.2 Proposed mechanistic pathway for the ring opening of epoxides to halohydrin and aminoalcohol by chromium(III) reagent

The proposed mechanism could be explained that the oxygen atom of epoxide coordinated to $CrCl_3.6H_2O$ or $Cr(NO_3)_3.9H_2O$ to form **A**, respectively. For the aliphatic terminal epoxides, ring opening reaction was highly regioselective in which the predominant attack of the nucleophile from the less hindered side of the epoxides (**B**) giving the corresponding 1-halo-2-alkanols or 1-alkylamino-2-alkanols (**D**). The only exception was the case of aromatic epoxide such as styrene oxide wherein 2-halo-2-phenylethanols or 2-alkylamino-2-phenylethanols (**E**) were obtained as the major product. In this case, the ring opening occurred *via* the preferential cleavage of the benzylic C-O bond provided a stabilized benzylic carbon species during the reaction (**C**).

CHAPTER IV

CONCLUSION

The aim of research is to investigate and to develop the new, simple, mild and efficient methodology for the ring opening of epoxides to more valuable and widely useful products with high yield and good selectivity using chromium reagents. The study was focused on the homogeneous system utilizing either $CrCl_3.6H_2O$ or $Cr(NO_3)_3.9H_2O$ which was disclosed to be new and quite effective reagent. The optimum conditions for the ring opening of epoxides to halohydrins are cyclohexene oxide 1 mmol as a substrate, $Cr(NO_3)_3.9H_2O$ 0.3 mmol as a reagent, lithium halide additive 5 mmol and THF 5 mL as a solvent at reflux for 1 h. The quantitative yield of the corresponding *trans*-2-halocyclohexanol was attained. Interestingly, $CrCl_3.6H_2O$ 1 mmol could be exclusively used as reagent under the same conditions leading to the formation of chlorohydrin in excellent yield within only 5 min., without any by-product formed and no additive required. In addition, the optimum conditions for the selective transformation of cyclohexene oxide into aminoalcohol are cyclohexene oxide 1 mmol as a substrate, $Cr(NO_3)_3.9H_2O$ 0.5 mmol as a reagent, amine 5 mmol as nucleophile and THF 5 mL as a solvent at reflux for 24 h. The high yield of the corresponding *trans*-2-alkylamino-cyclohexanol was obtained. The several advantages such as high catalytic activities and reactivities, stable in air and moisture, low cost, commercially available, rapid reaction rate and simplify in the experimental was made these reagents applicable. In addition, there was no report on the utilization of these chromium reagents for catalytic ring opening of epoxide into halohydrins and aminoalcohols.

The developed ring opening system was also applicable to other epoxides and amines, in case of aminoalcohol synthesis. Applications on the ring opening of alkyl- and aryl-substituted epoxides were fruitfully achieved and gave the desired products in high

to quantitative yield with excellent selectivity. For 1-dodecene oxide, the halohydrin and aminoalcohol which derived from the attack of halide or amino nucleophiles on the less hindered side of the epoxide were formed as the major product in high yield. Interestingly, in case of butyl glycidyl ether, *tert*-butyl glycidyl ether and phenyl glycidyl ether, the oxygen atom on the epoxide ring affected the formation of halohydrin. The attack of the halide on the less hindered side of the epoxide furnished only single product. For aryl-substituted epoxides, for example styrene oxide, the mechanistic pathway of this ring opening to give a mixture of bromohydrins or aminoalcohol included the attack of Br^- or amine nucleophiles on the benzylic position of the epoxide as the main constituent in high to quantitative yield. In addition, the applications on the developed ring opening system to alkyl- and aryl-amines were also achieved and gave the desired products in moderate to high yield. In this case, electron-withdrawing group made low electron density of aromatic amine and limited its reactivity to assist the formation of the corresponding aminoalcohol.

Furthermore, the notable features of this procedure make it a useful and attractive process for other benefit compound synthesis, for example, alkoxyalcohol. The formation of the corresponding alkoxyalcohol was obtained in excellent yield. In addition, the results also emphasize the versatility of this procedure to synthesize nitrate ester which has many advantages in organic synthesis. This study was also focused on the competitive reactivity of nucleophile which indicated bromide was superior in reactivity than chloride nucleophile.

Proposal for the future work

This research concerned with the new methodology development for the selective ring opening of epoxides by chromium reagents. The outcome opened many possibilities to deal with future exploration. A commercially available $CrCl_3.6H_2O$ and $Cr(NO_3)_3.9H_2O$ has never been utilized for the epoxides ring opening, therefore the substitution of this reagent in the use of other reagents may provide other intriguing results in terms of product yield and selectivity. From the academic view point, bioactive compounds and pharmaceutically active compounds containing chiral center are interesting to synthesize starting from epoxides under developed conditions. Besides, the

Friedel-Crafts alkylation of indoles by catalytic $RuCl_3.nH_2O$ or sulfated zirconia has been reported [60] leading to 3-alkylated derivatives occurred *via* epoxide ring opening reaction. The exploration of $CrCl_3.6H_2O$ and $Cr(NO_3)_3.9H_2O$ for the manipulation of this Friedel-Crafts alkylation reaction should be another interesting point. Moreover, a variety of epoxide, for example allylic or vinylic epoxide, should be cautiously investigated. This present examination is a profitable example for the methodology in crucial chemical reaction nowadays, and may be the one of valuable chemical processes in the near future.

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APPENDICES

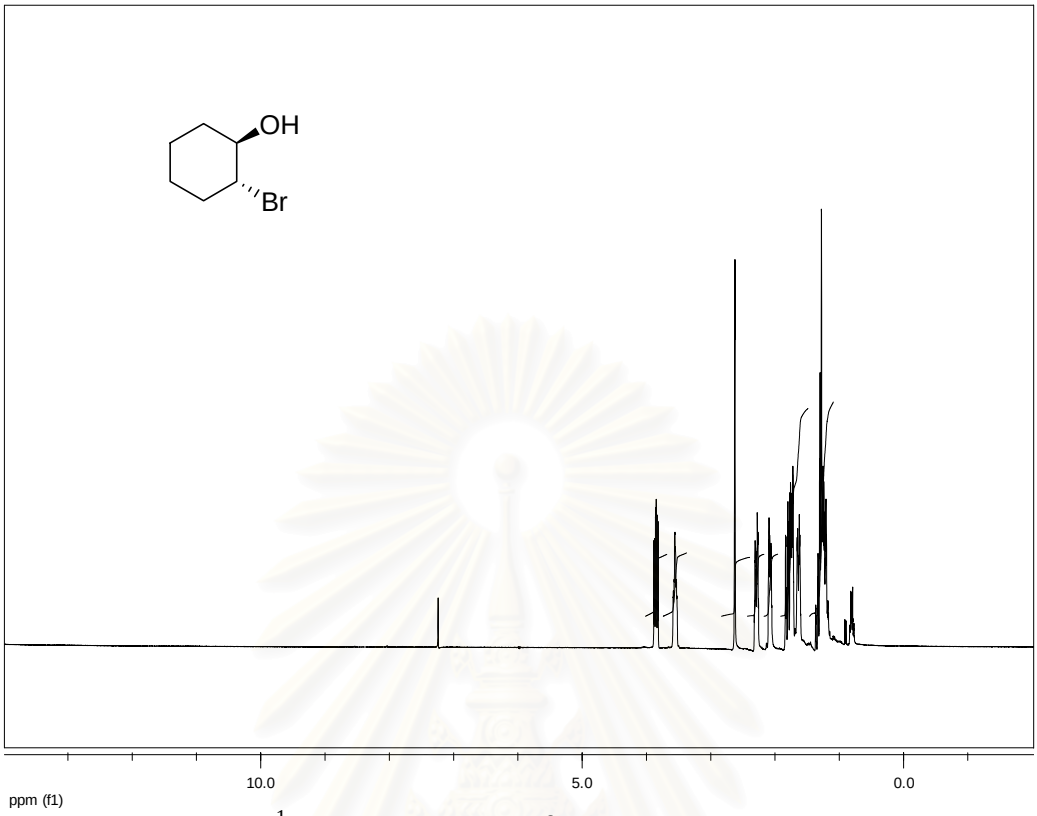


Figure A1 The ^{1}H-NMR spectrum of *trans*-2-bromocyclohexanol (**3**)

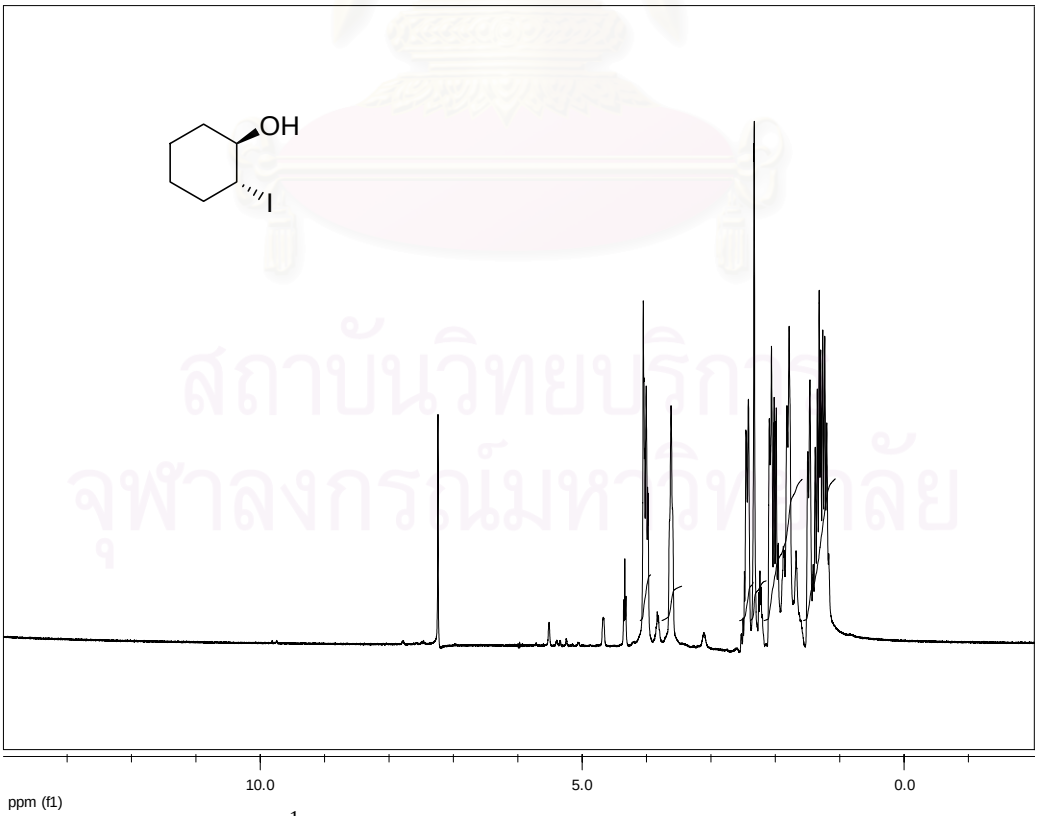


Figure A2 The ^{1}H-NMR spectrum of *trans*-2-iodocyclohexanol (**4**)

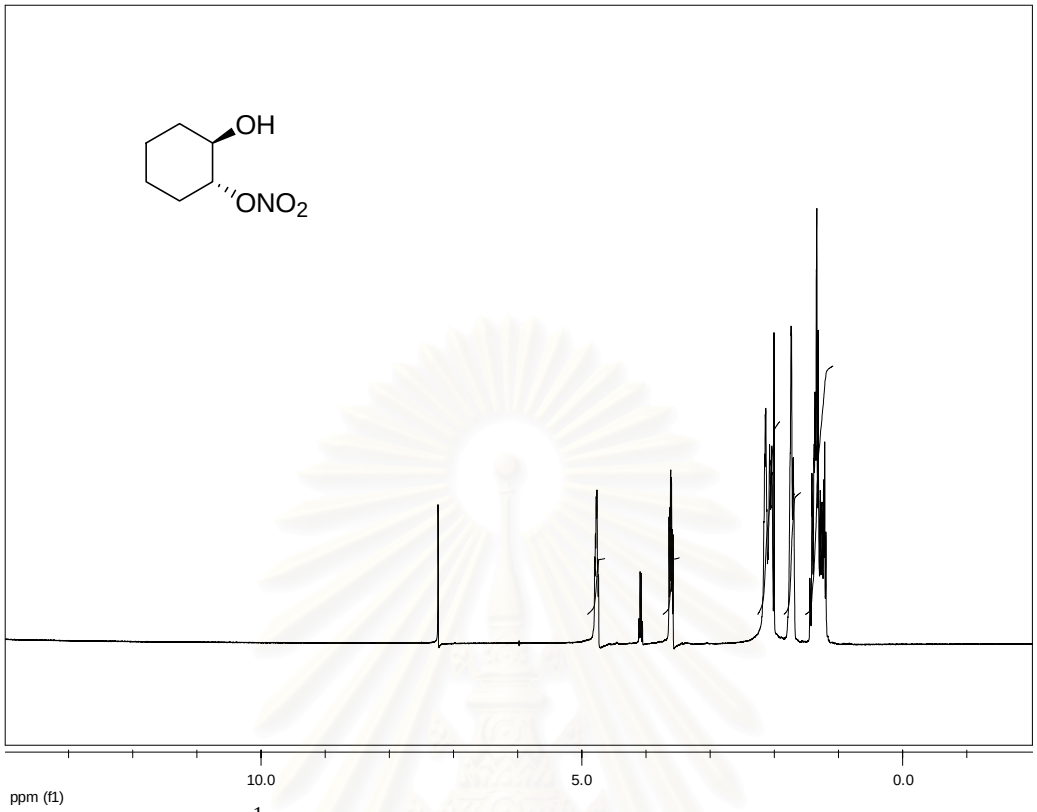


Figure A3 The ^{1}H-NMR spectrum of *trans*-2-nitroxycyclohexan-1-ol (**5**)

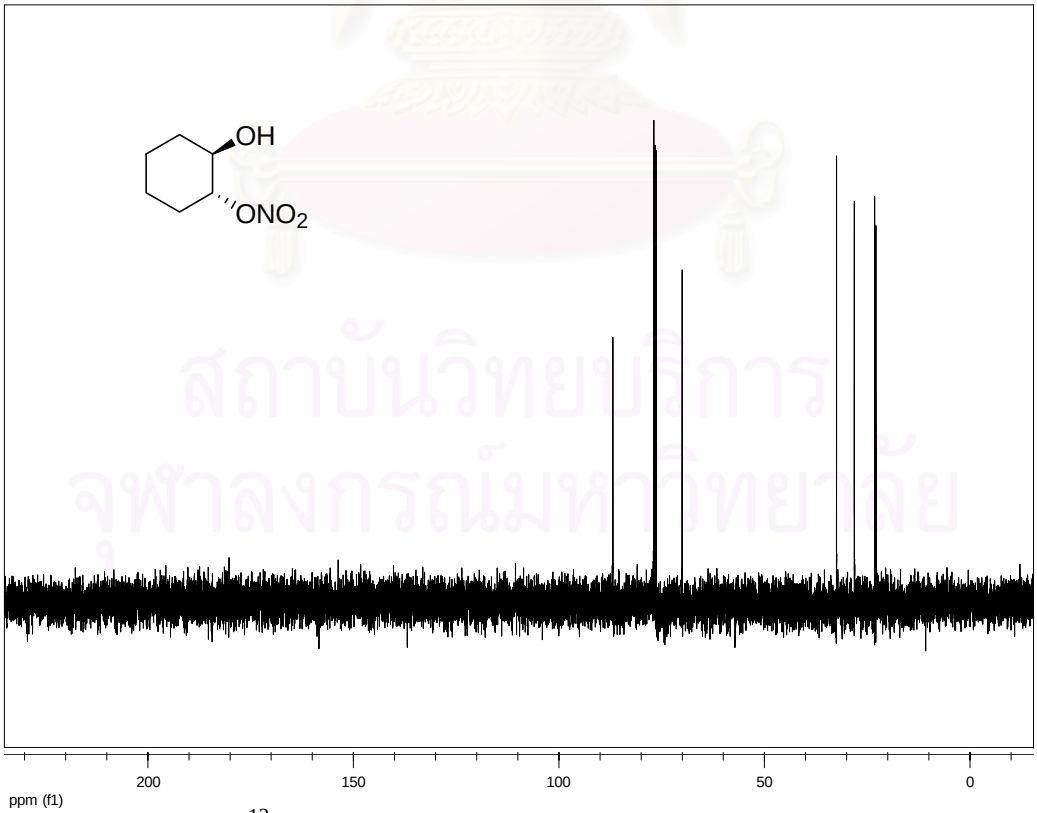


Figure A4 The ^{13}C-NMR spectrum of *trans*-2-nitroxycyclohexan-1-ol (**5**)

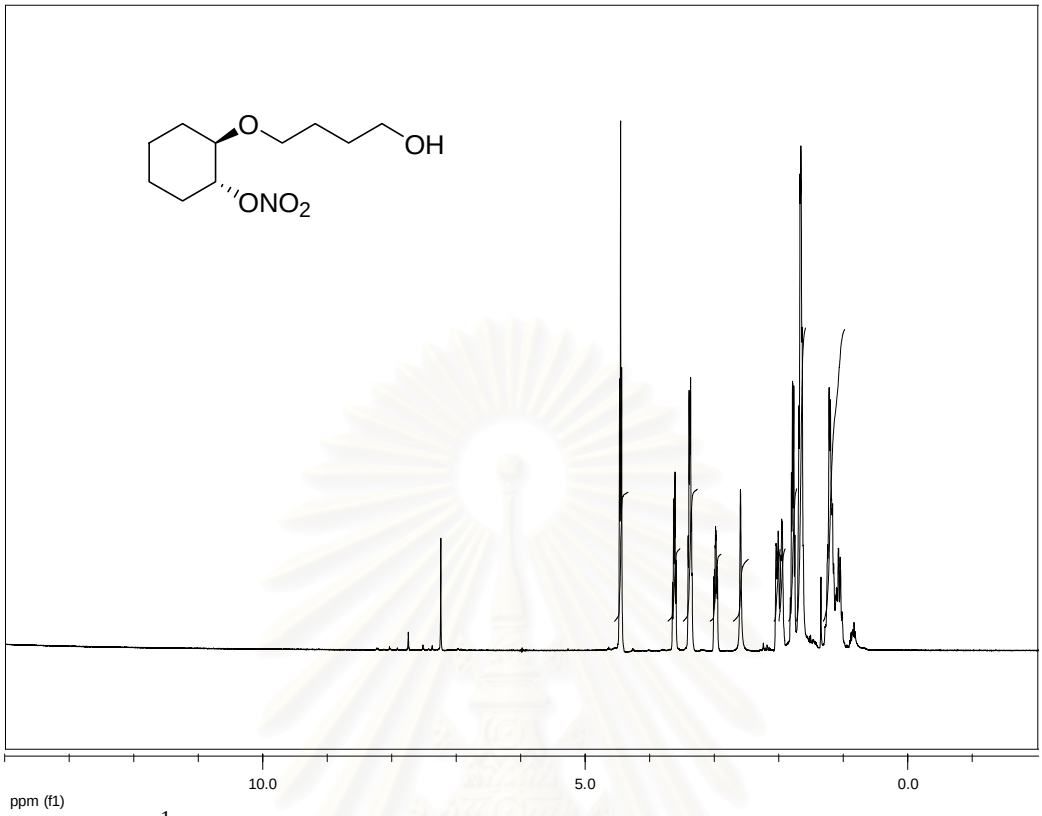


Figure A5 The ^{1}H-NMR spectrum of *trans*-4-(2-Nitroxy-cyclohexyloxy)-butan-1-ol (**6**)

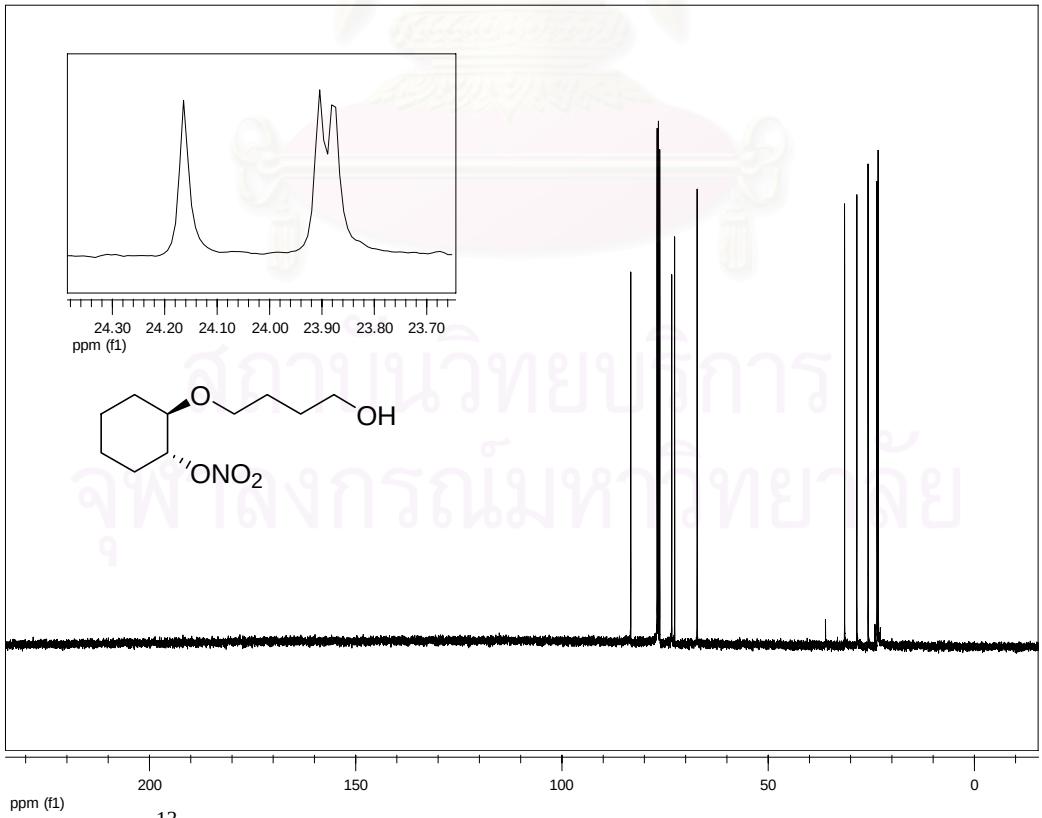


Figure A6 The ^{13}C-NMR spectrum of *trans*-4-(2-Nitroxy-cyclohexyloxy)-butan-1-ol (**6**)

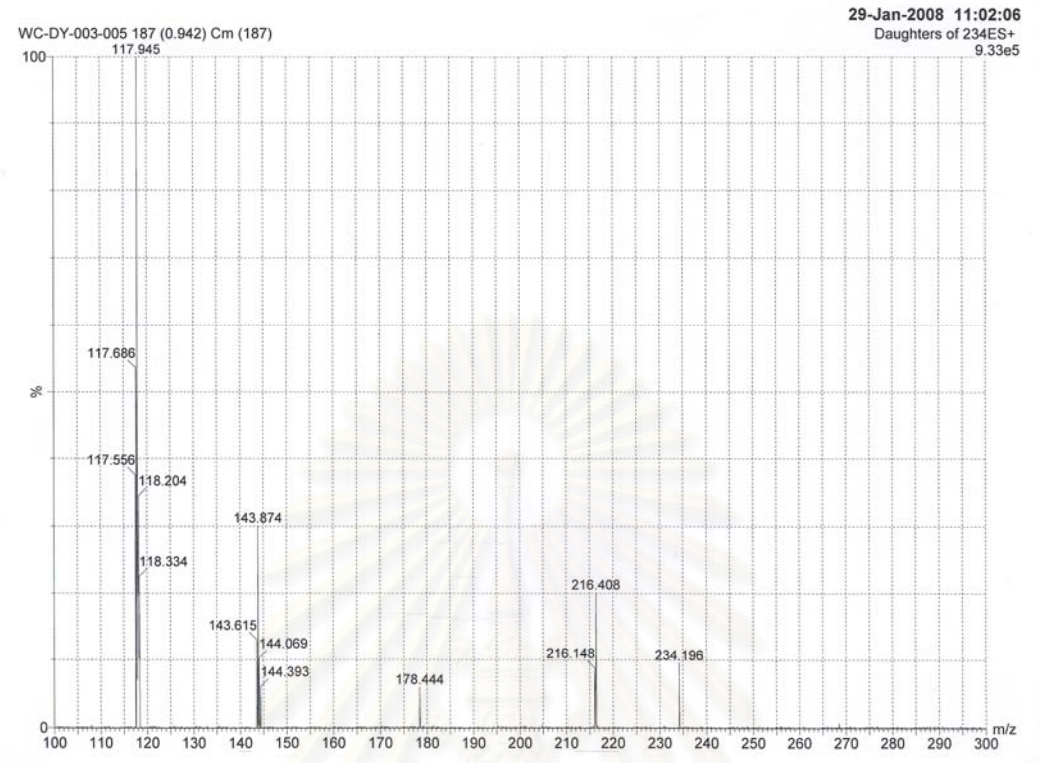
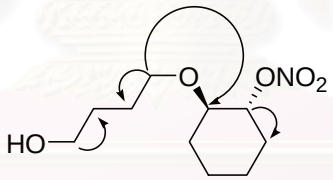
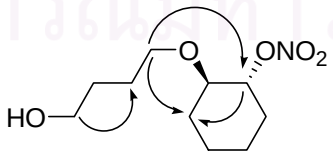


Figure A7 The mass spectrum of compound **6**



The COSY spectrum of **6** (Figure A8) reasonably exposed correlations between H-1 (δ_H 4.46-4.49) and H-2 (δ_H 1.78-1.85), between H-4 (δ_H 3.37-3.43) and H-3 (δ_H 1.65-1.72), H-1' (δ1.96) and H-2' (δ_H 2.98-3.04) and H-3' (δ_H 2.04-2.07 and 1.05-1.32), respectively.



According to the HMBC spectrum (Figure A9), it was clearly manifested the correlations between C-1 (δ_C 73.10) and H-3, between C-4 (δ_C 73.81) and H-2' and H-6', between C-2' (δ_C 83.71) and H-6', respectively.

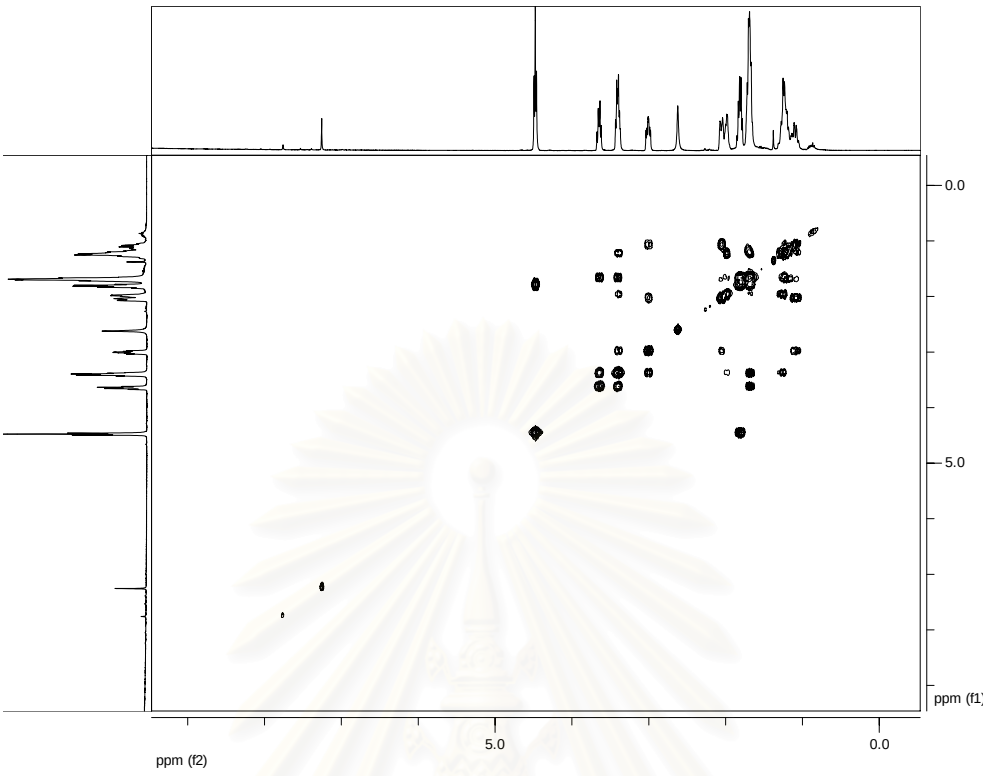


Figure A8 The COSY spectrum of Compound **6**

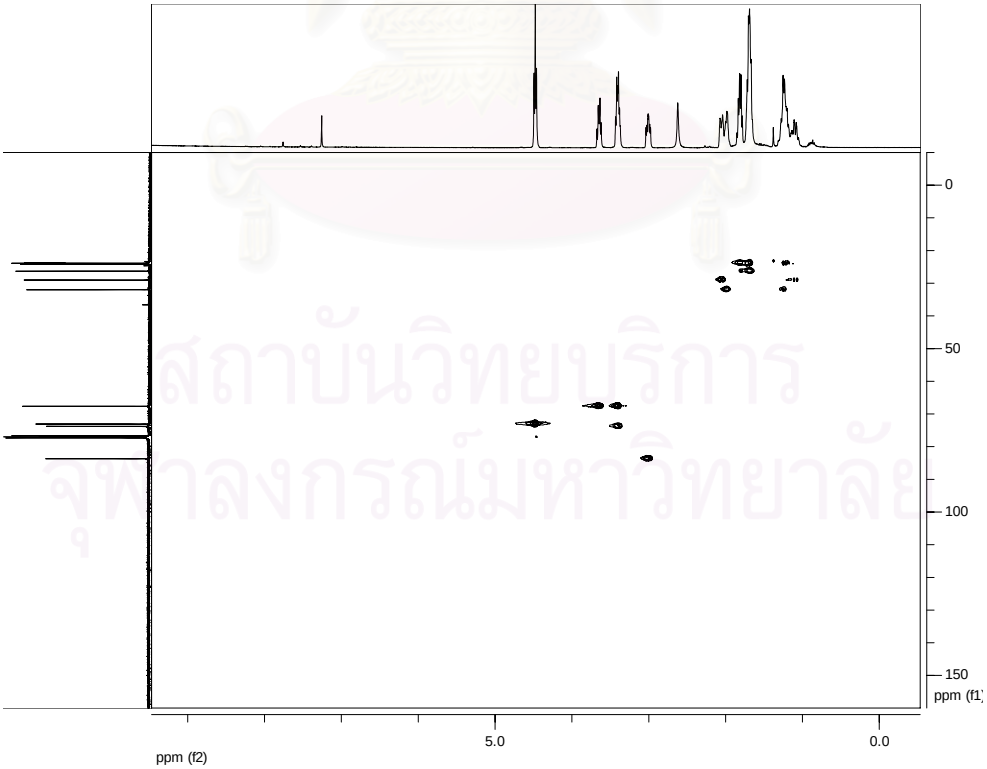


Figure A9 The HMQC spectrum of Compound **6**

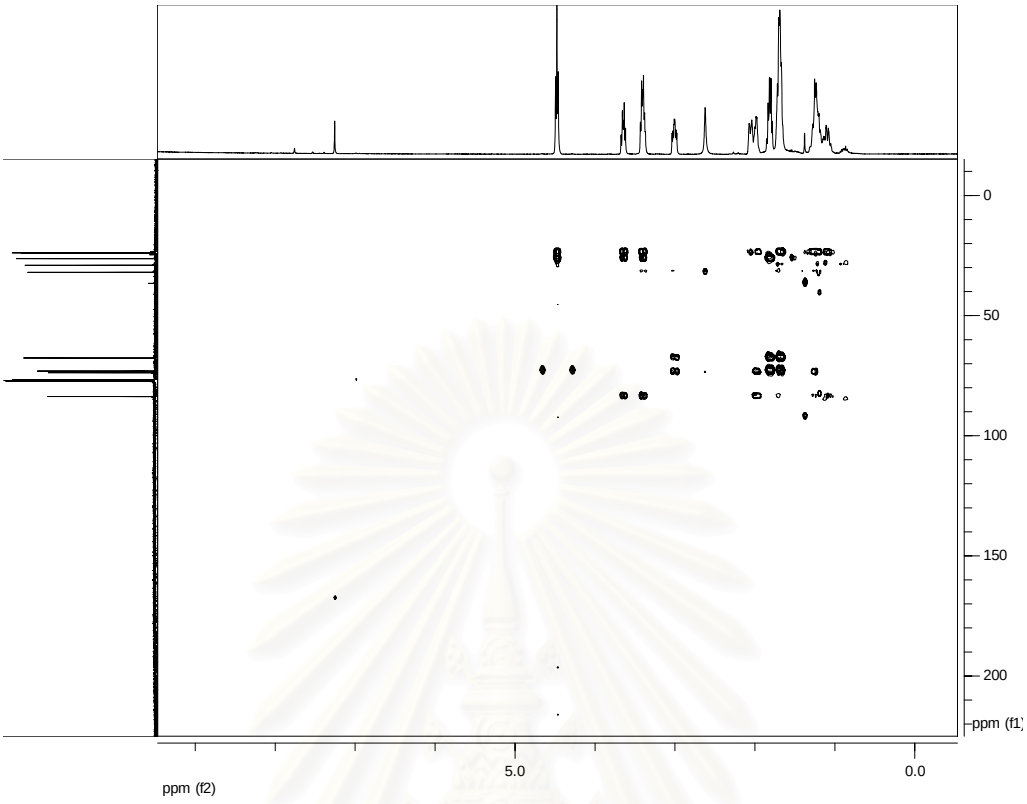


Figure A10 The HMBC spectrum of Compound **6**

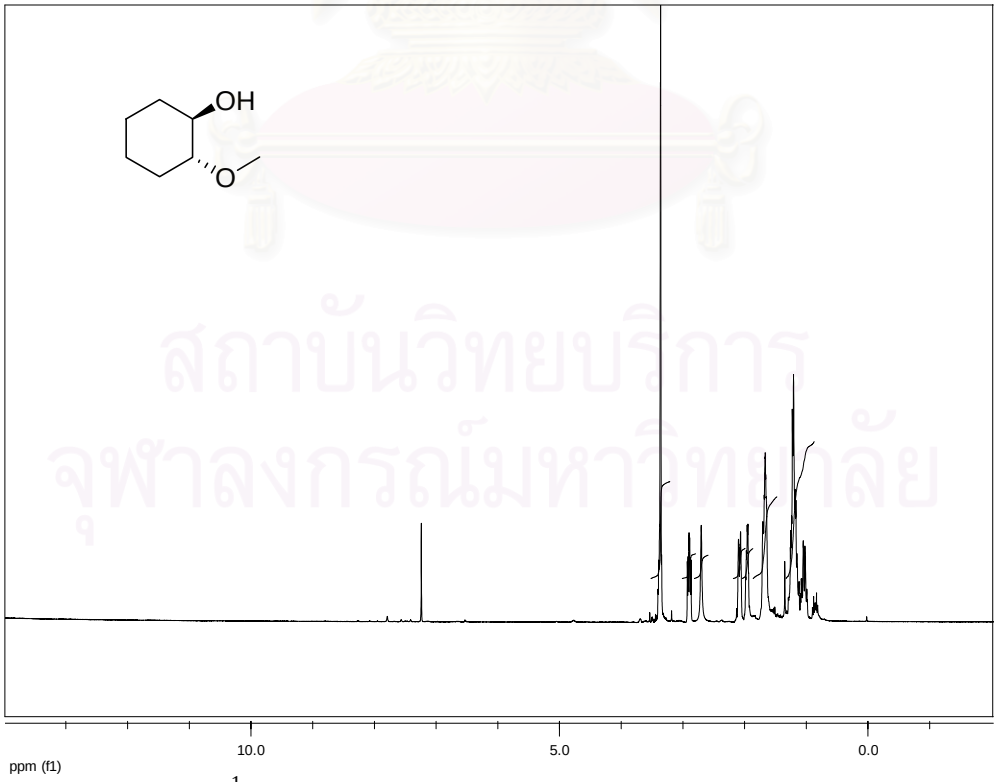


Figure A11 The ^{1}H-NMR spectrum of *trans*-2-methoxycyclohexan-1-ol (**7**)

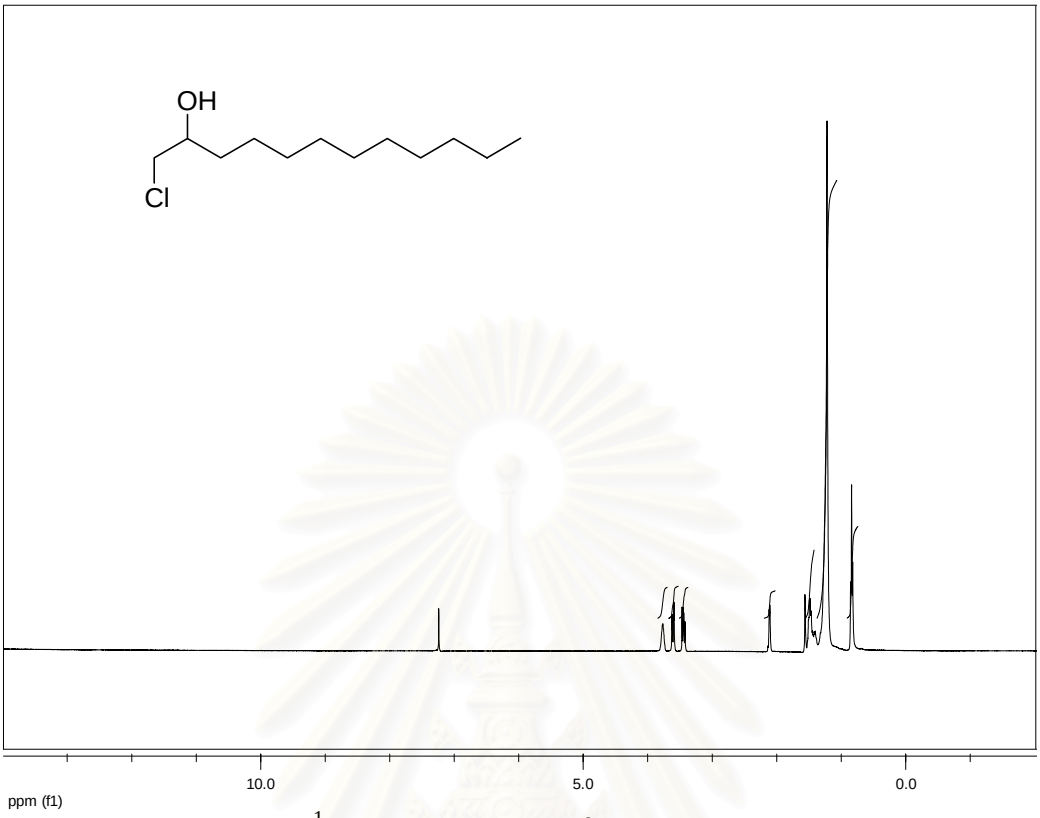


Figure A12 The ^{1}H-NMR spectrum of 1-chlorododecan-2-ol (**9A**)

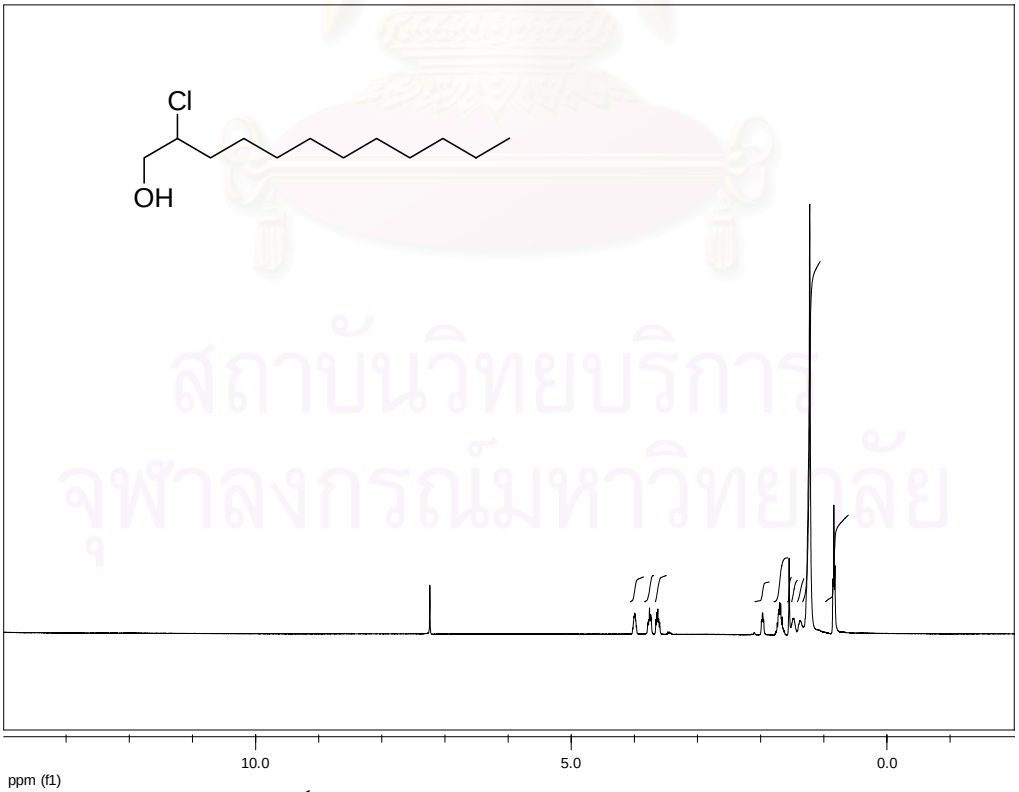


Figure A13 The ^{1}H-NMR spectrum of 2-chlorododecan-1-ol (**9B**)

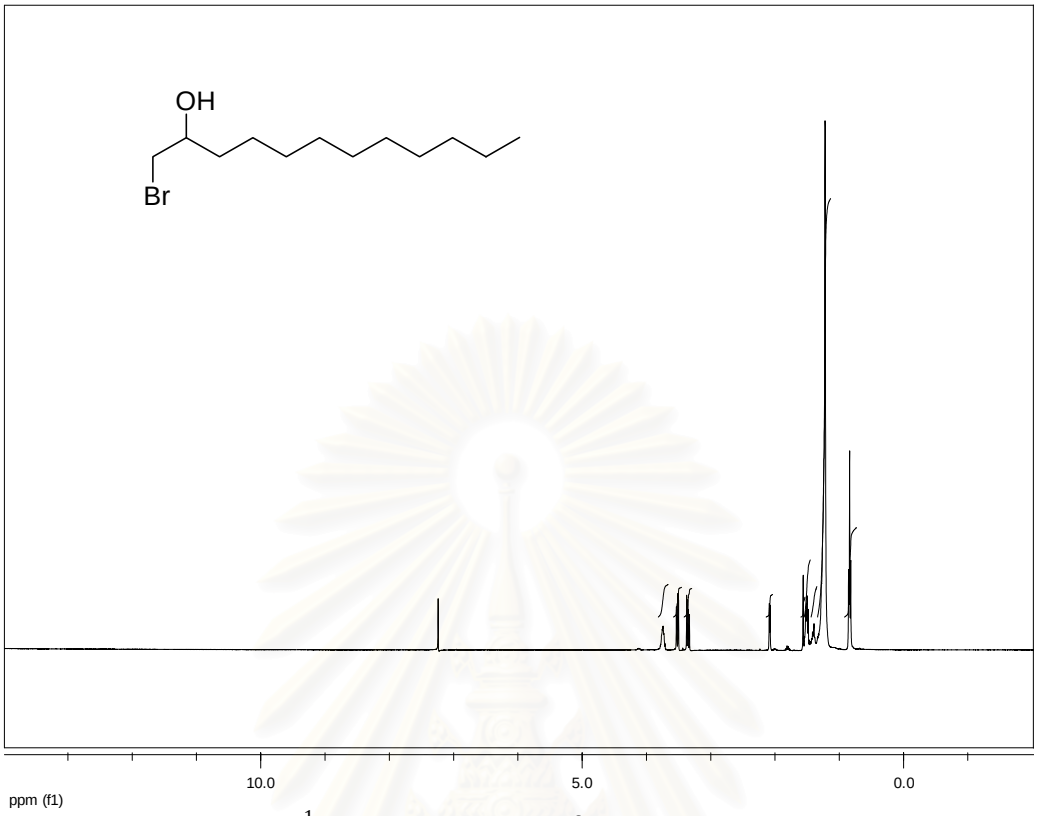


Figure A14 The ^{1}H-NMR spectrum of 1-bromododecan-2-ol (**10A**)

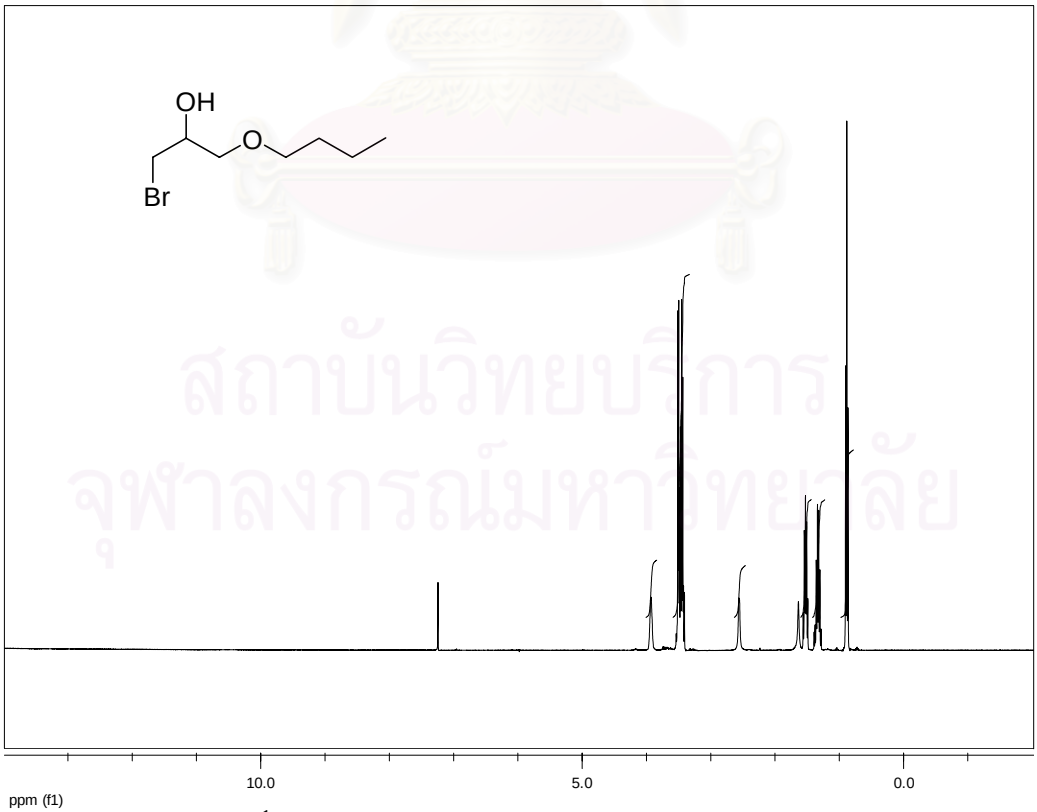


Figure A15 The ^{1}H-NMR spectrum of 1-bromo-3-butoxypropan-2-ol (**13**)

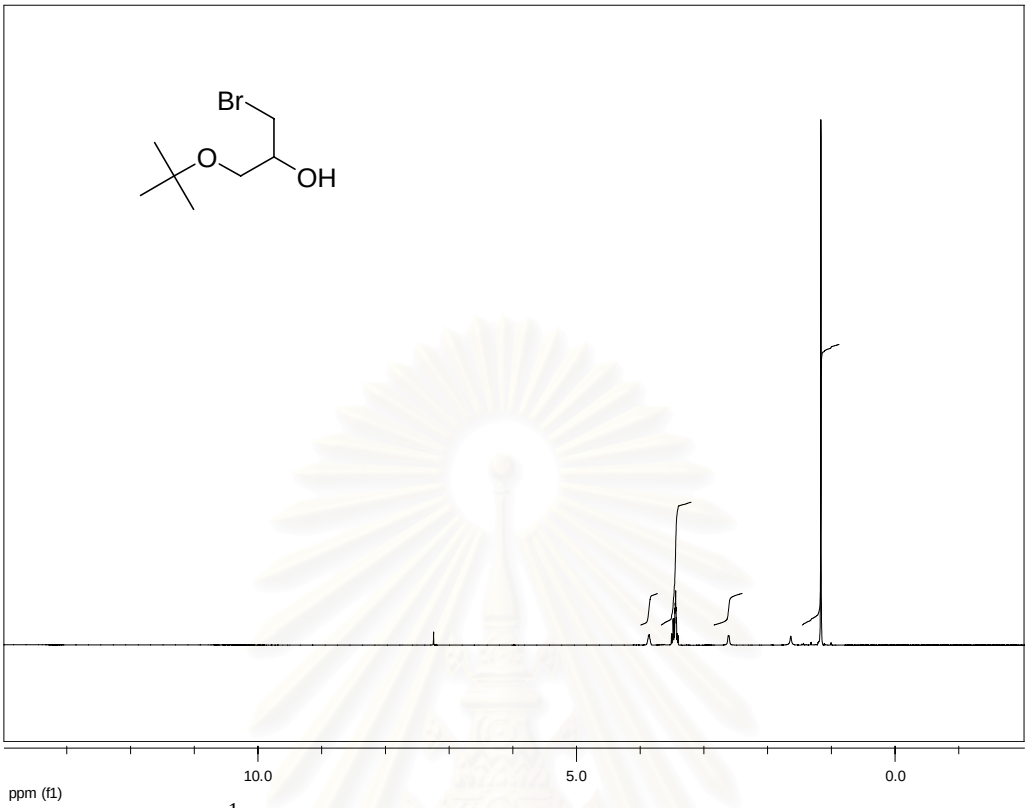


Figure A16 The ^{1}H-NMR spectrum of 1-bromo-3-*tert*-butoxypropan-2-ol (**15**)

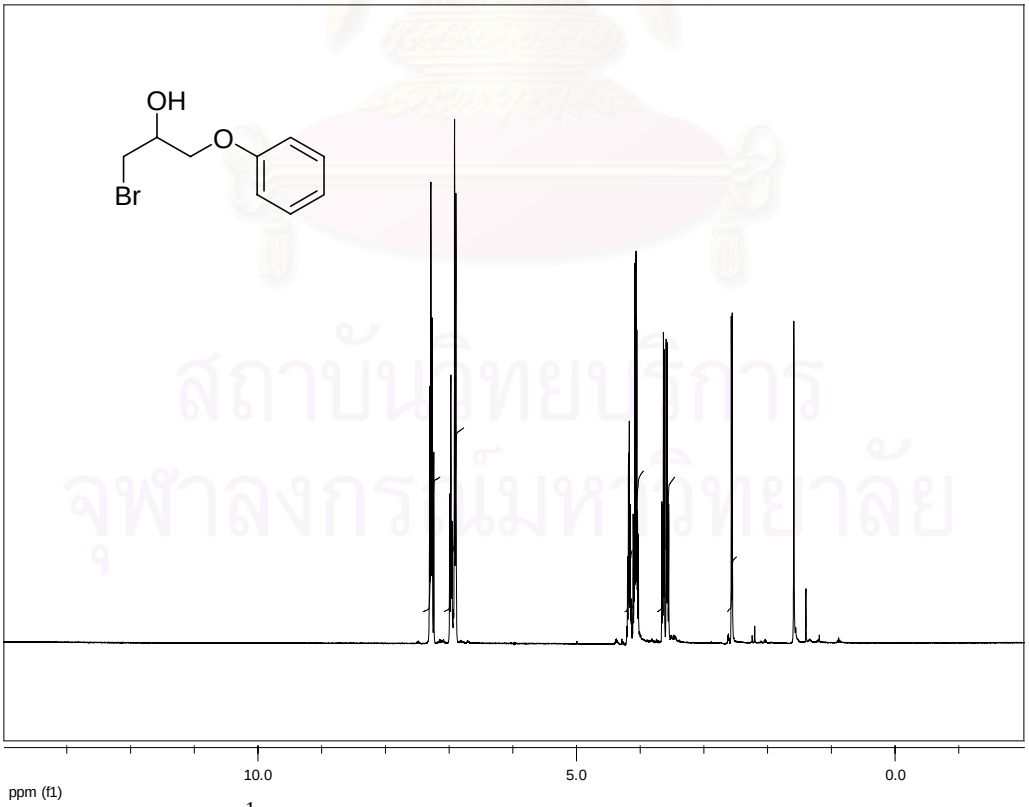


Figure A17 The ^{1}H-NMR spectrum of 1-bromo-3-phenoxypropan-2-ol (**17**)

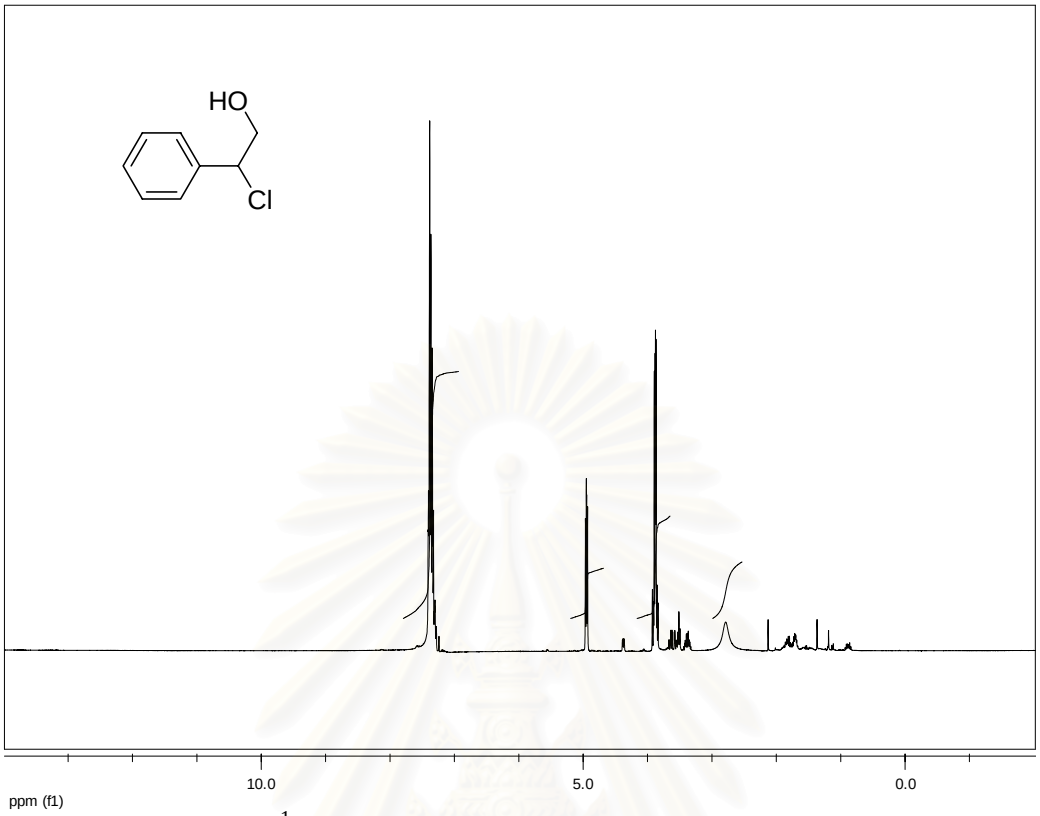


Figure A18 The ^{1}H-NMR spectrum of 2-chloro-2-phenylethanol (**19A**)

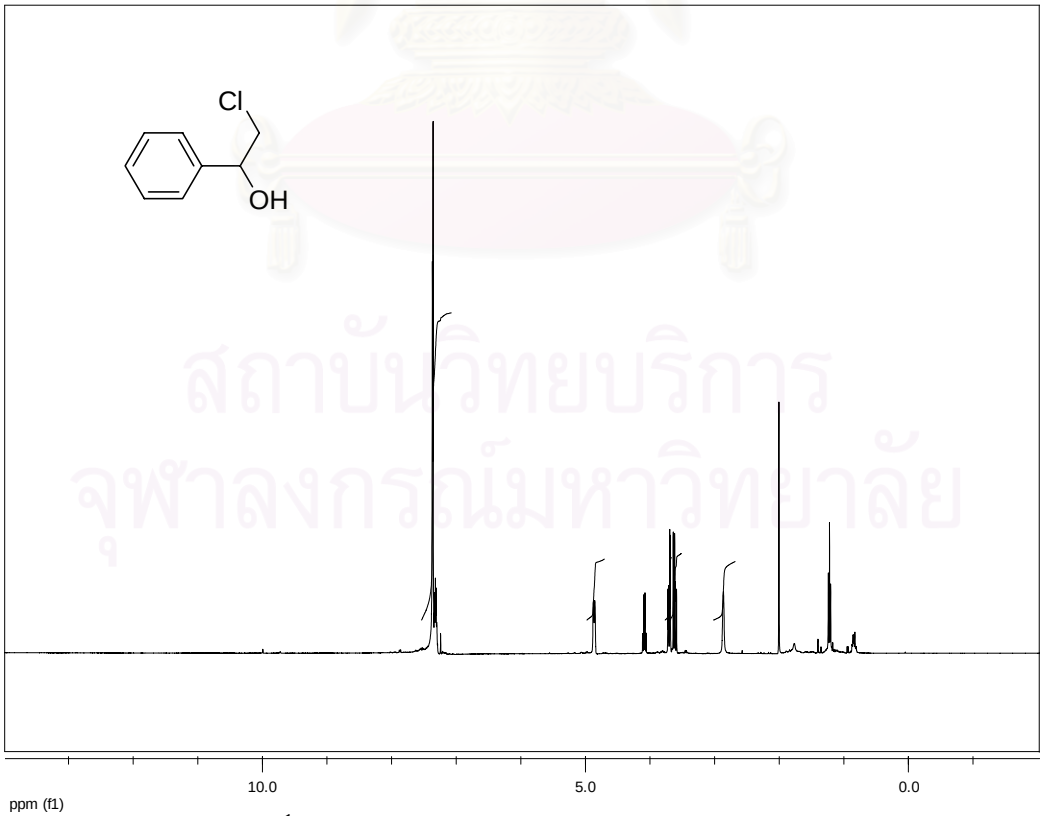


Figure A19 The ^{1}H-NMR spectrum of 2-chloro-1-phenylethanol (**19B**)

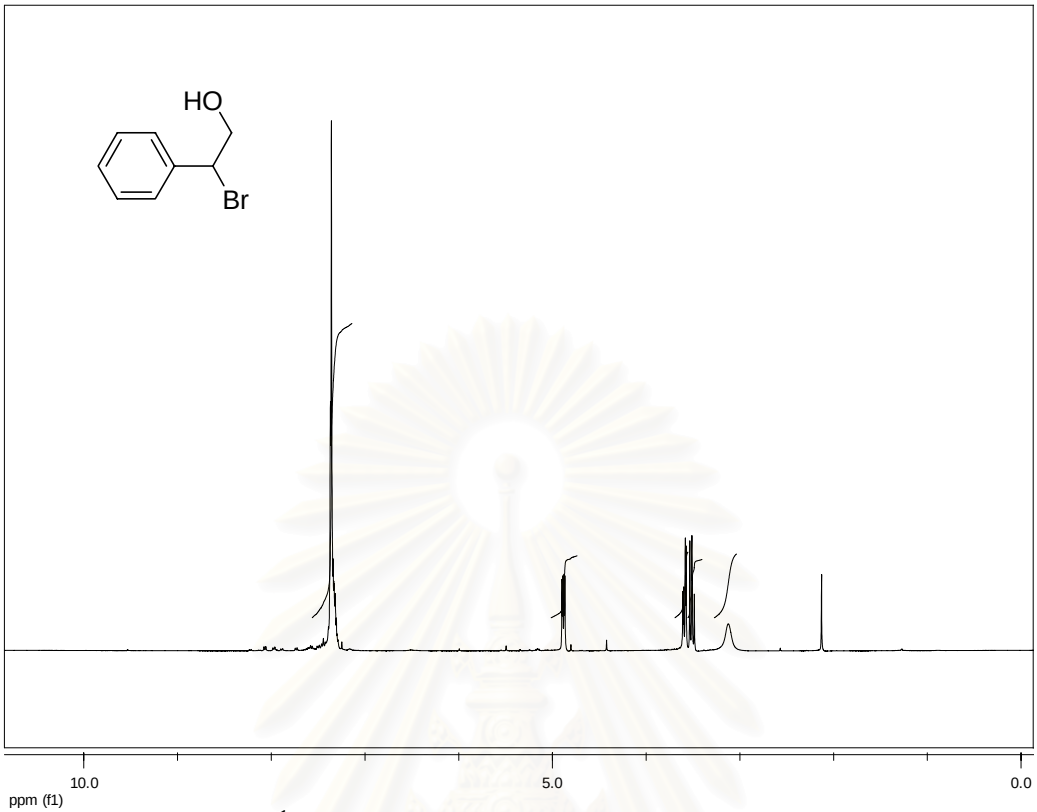


Figure A20 The ^{1}H-NMR spectrum of 2-bromo-2-phenylethanol (**20A**)

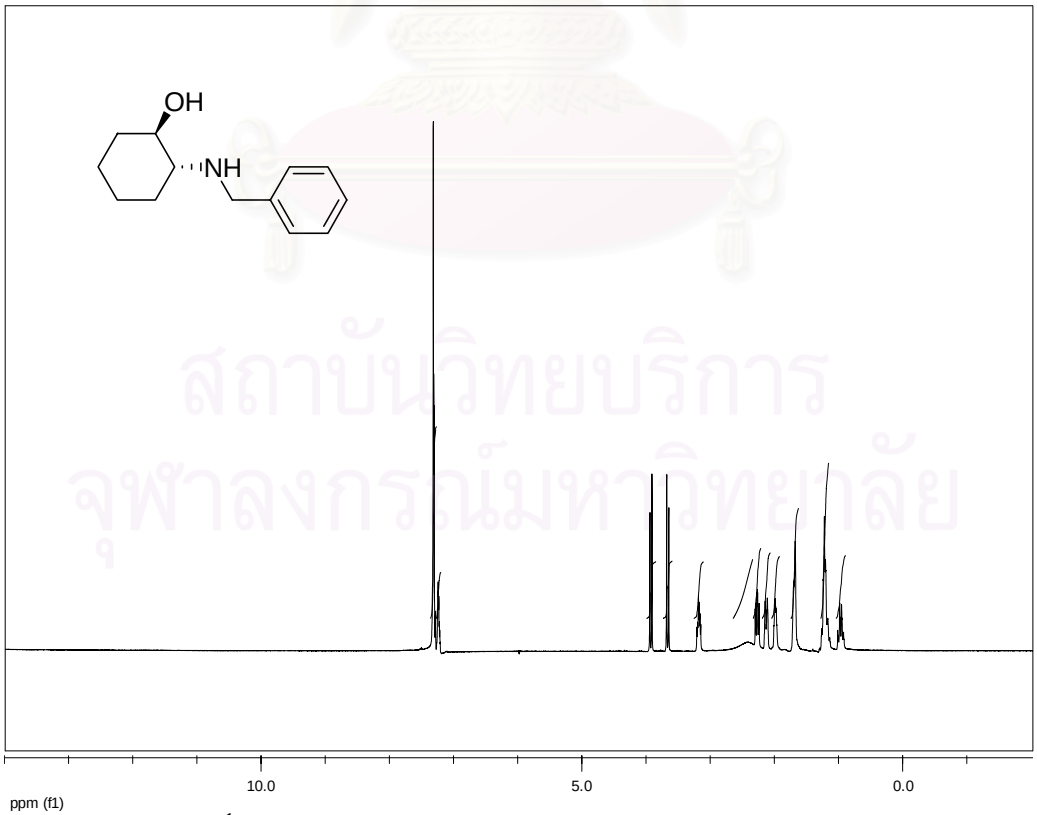


Figure A21 The ^{1}H-NMR spectrum of *trans*-2-(benzylamino)cyclohexanol (**24**)

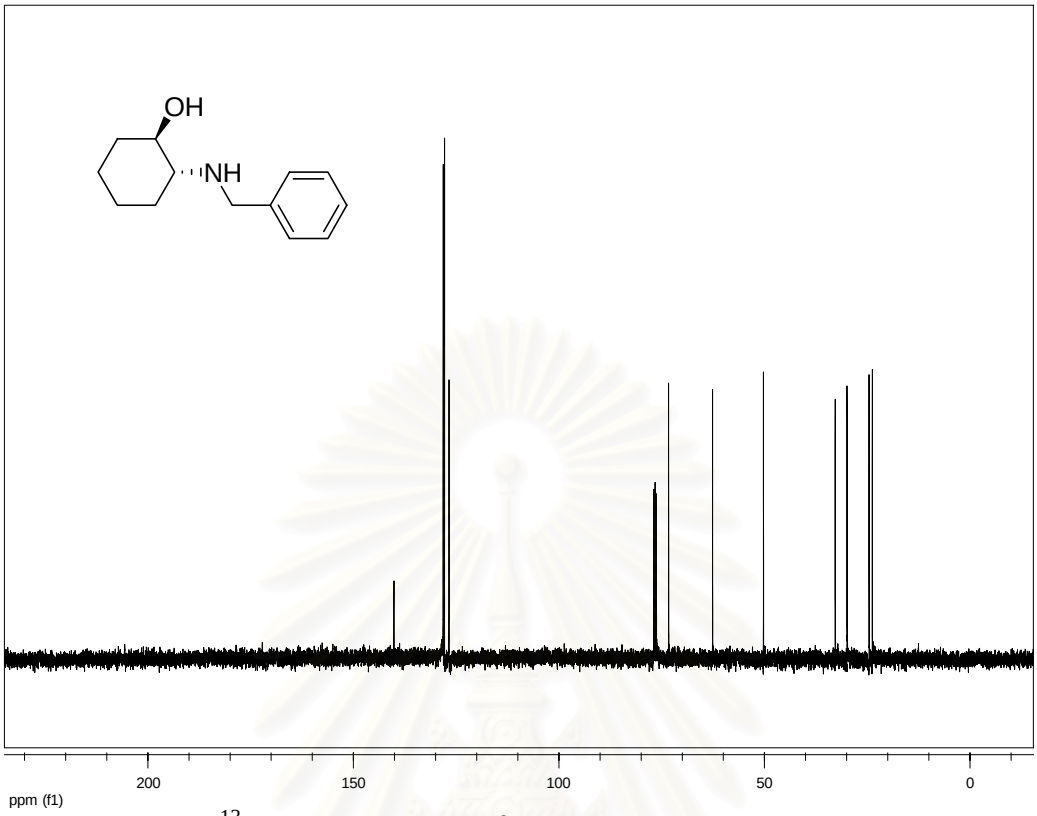


Figure A22 The ^{13}C-NMR spectrum of *trans*-2-(benzylamino)cyclohexanol (**24**)

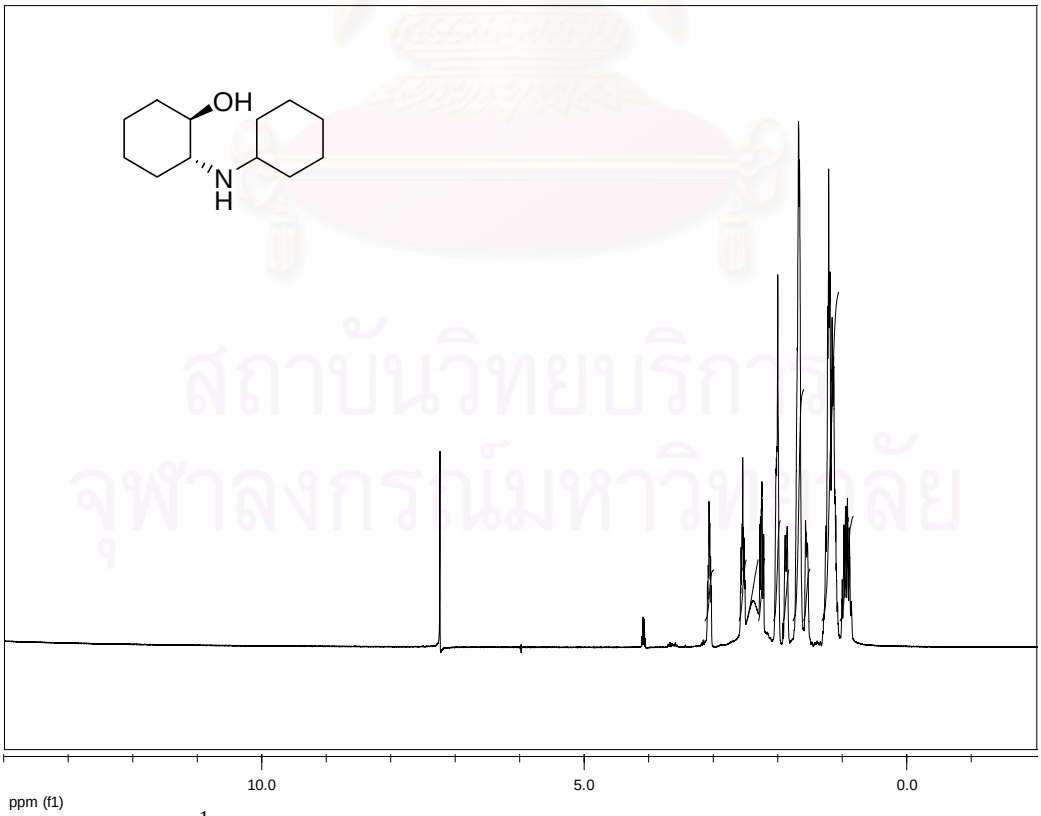


Figure A23 The ^{1}H-NMR spectrum of *trans*-2-(cyclohexylamino)cyclohexanol (**25**)

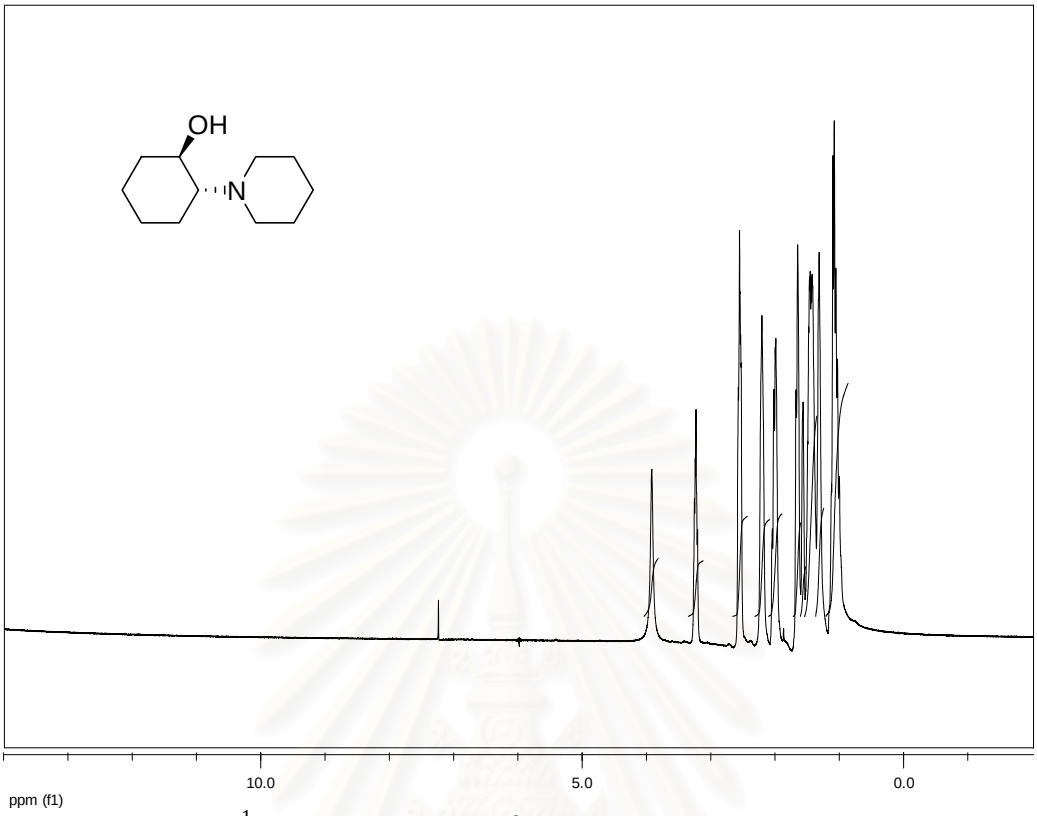


Figure A24 The ^{1}H-NMR spectrum of *trans*-2-(piperidino)cyclohexanol (**26**)

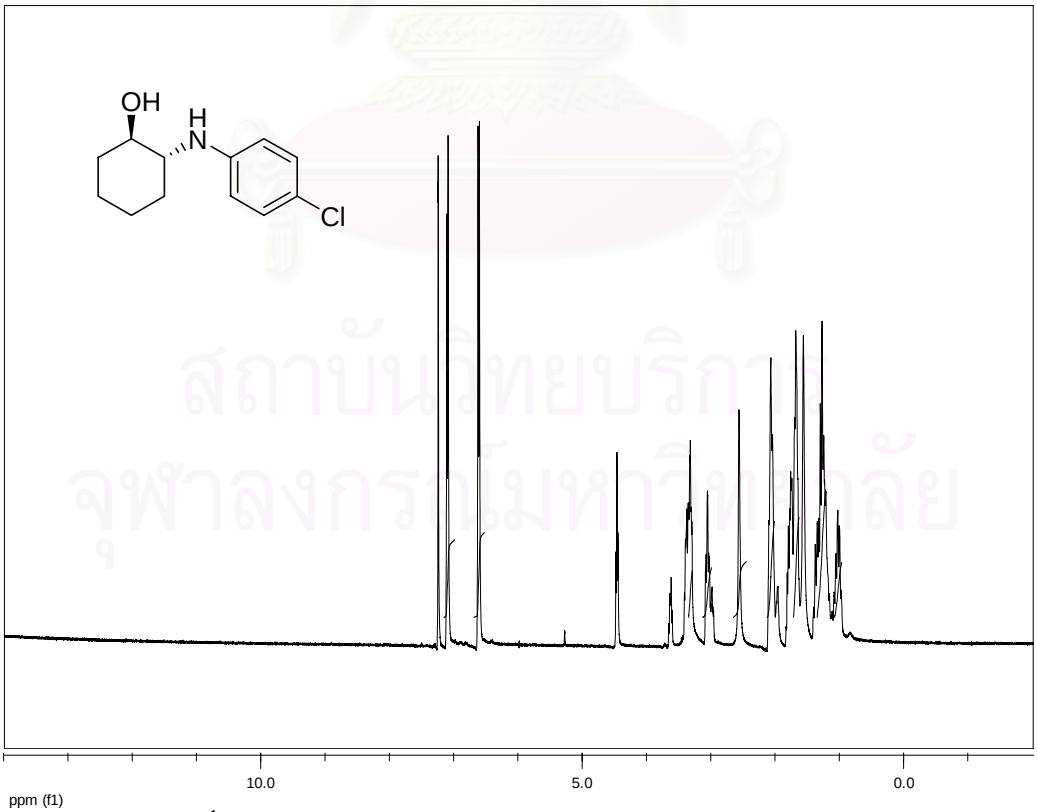


Figure A25 The ^{1}H-NMR spectrum of *trans*-2-(4-chloroanilino)cyclohexanol (**28**)

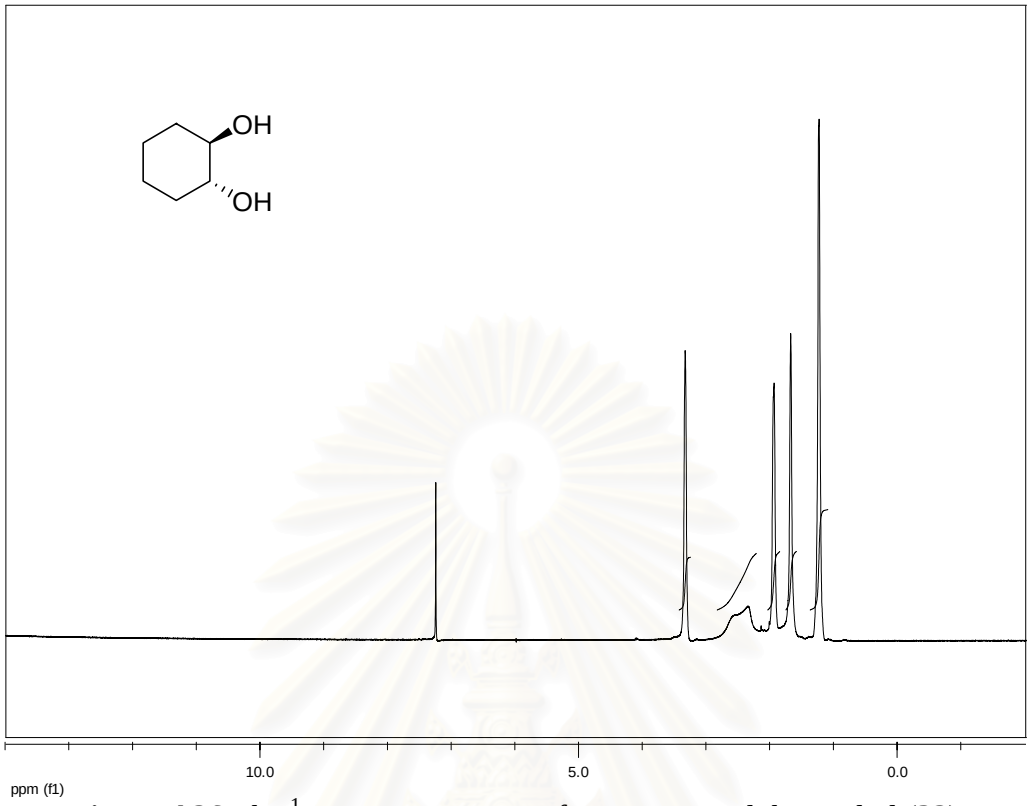


Figure A26 The ^{1}H-NMR spectrum of *trans*-1,2-cyclohexandiol (**32**)

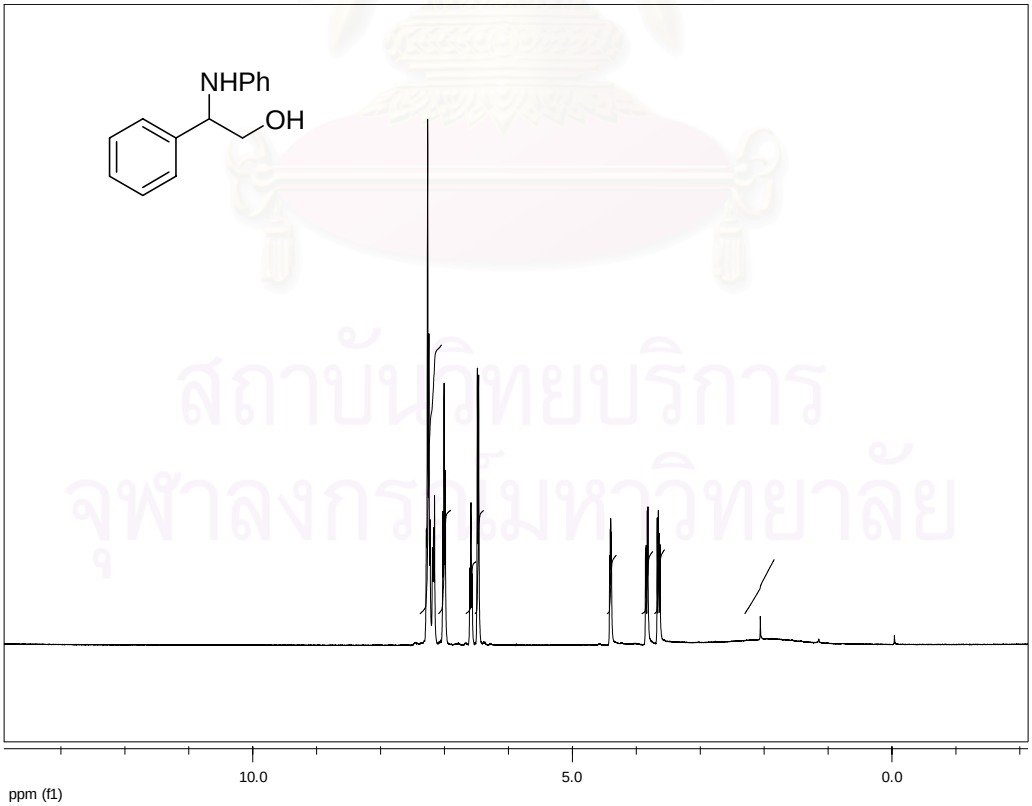


Figure A27 The ^{1}H-NMR spectrum of 2-anilino-2-phenyl-1-ethanol (**33A**)

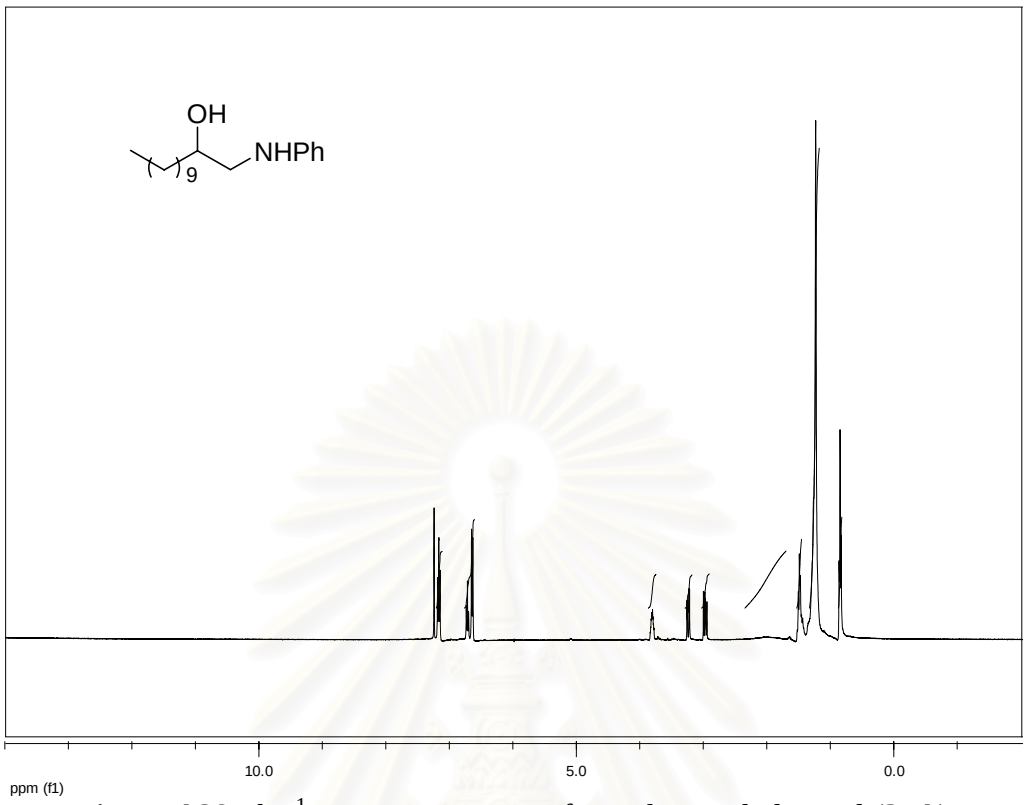


Figure A28 The ^{1}H-NMR spectrum of 2-anilino-2-dodecanol (**34A**)

VITA

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