การจัดตัวใหม่ของอิพ็อกไซด์โดยใช้เกลือโลหะแทรนซิชันในไอออนิกลิควิด

นางสาววรรณพร ประกอบกิจ

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REARRANGEMENT OF EPOXIDES BY TRANSITION METAL SALTS IN IONIC LIQUID

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วรรณพร ประกอบกิจ : การจัดตัวใหม่ของอิพ็อกไซด์โดยใช้เกลือโลหะแทรนซิชันในไอออนิกลิควิด (REARRANGEMENT OF EPOXIDES BY TRANSITION METAL SALTS IN IONIC LIQUID) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ดร.วรินทร ชวศิริดร., 68 หน้า.

ได้พัฒนาระบบปฏิกิริยาใหม่ที่มีประสิทธิภาพสำหรับการจัดตัวใหม่ของแอริลอิพ็อกไซด์โดยสารประกอบเชิงซ้อนนิกเกิลในอิมิดาโซลไอออนิกลิควิด ได้ศึกษาชนิดของนิกเกิล ชนิดของไอออนิกลิควิด อุณหภูมิและระยะเวลาในการทำปฏิกิริยาเพื่อหาภาวะที่เหมาะสม การจัดตัวใหม่ของสไตรีนออกไซด์กับ $NiBr_2 \cdot 3H_2O$ และ $NiBr_2$ ที่ปราศจากน้ำในไอออนิกลิควิด 1- เฮกซิล-3-เมทิลอิมมิดาโซเลียมโบรไมด์ ([hmim][Br]) ที่อุณหภูมิ 120 องศาเซลเซียส ระยะเวลา 15 นาที ให้ร้อยละผลได้ 76 และ 84 ของเฟนิลแอซิทัลดีไฮด์ตามลำดับ การประยุกต์ปฏิกิริยาจัดตัวใหม่ของแอริลอีพ็อกไซด์อื่นๆ ให้ผลิตภัณฑ์ในปริมาณปานกลางถึงสูงและมีความจำเพาะเจาะจงผ่านการย้ายหมู่ไฮไดรด์ ได้ทดสอบประสิทธิภาพของ $NiBr_2 \cdot 3H_2O$ /[hmim][Br] ที่ปราศจากการเติมเกลือนิกเกิลกับการใช้ซ้ำ 5 ครั้งของสารอัลฟ่าเมทิลสไตรีนออกไซด์ อย่างไรก็ตามการนำกลับมาใช้ซ้ำของ $NiBr_2 \cdot 3H_2O$/[hmim][Br] กับสไตรีนออกไซด์ให้ผลไม่เป็นที่น่าพอใจ $NiBr_2$ ที่ปราศจากน้ำสามารถแก้ไขปัญหานี้ นอกจากนี้การใช้ไมโครเวฟช่วยในการจัดตัวใหม่ของสไตรีนออกไซด์กับ $NiBr_2$ ที่ปราศจากน้ำใน [hmim][Br] ที่อุณหภูมิ 90 องศาเซลเซียสเป็นระยะเวลา 5 นาที ให้ร้อยละผลได้ 85 นำไอออนิกลิควิดกลับมาใช้ซ้ำพบว่าสามารถได้สามครั้งโดยประสิทธิภาพไม่ลดลง

สาขาวิชา   ปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์   ลายมือชื่อนิสิต ....

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WANNAPORN PRAKOBKICH: REARRANGEMENT OF EPOXIDES BY TRANSITION METAL SALTS IN IONIC LIQUID. ADVISOR: ASST. PROF. WARINTHORN CHAVASIRI, Ph.D., 68 pp.

A new and efficient system for the rearrangement of aryl epoxides by nickel complexes in imidazolium ionic liquids has been developed. Types of nickel complexes, ionic liquids, reaction temperature and reaction time were optimized. The rearrangement of styrene oxide with $NiBr_2 \cdot 3H_2O$ and anhydrous $NiBr_2$ in 1-hexyl-3-methylimidazolium bromide ([hmim][Br]) at $120^{\circ}C$ for 15 min provided 76 and 84% yield of phenylacetaldehyde, respectively. Applications on the rearrangements of aryl-substituted epoxides were fruitfully achieved yielding desired products in moderate to high yield and excellent selectivity *via* hydride migration. The activity of the reused $NiBr_2.3H_2O$/[hmim][Br] was tested in subsequent runs without addition of fresh catalyst for five runs on α-methylstyrene oxide. However, the reuse of $NiBr_2.3H_2O$/[hmim][Br] with styrene oxide gave unsatisfactory result. Anhydrous $NiBr_2$ could be used to solve this problem. Moreover, the aids of microwave for the rearrangement of styrene oxide with anhydrous $NiBr_2$ in [hmim][Br] at $90\ ^{\circ}C$ for 5 min provided 85% yield of the target product. Very good reusability of the recovered ionic liquid without significant loss of the activity was observed within three subsequent runs.

Field of Study:	Petrochemistry and Polymer Science	Student's Signature	....
		Advisor's Signature	....
Academic Year:	2015		

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LIST OF ABBREVIATIONS

Acac	acetylacetonate
anh	anhydrous
[bmim][Br]	1-butyl-3-methylimidazolium bromide (ionic liquid)
[bmim][BF$_4$]	1-butyl-3-methylimidazolium tetrafluoroborate (ionic liquid)
[bmim][PF$_6$]	1-butyl-3-methylimidazolium hexafluorophosphate (ionic liquid)
δ	chemical shift
J	coupling constant (NMR)
cm^{-1}	unit of wavelength
$^{\circ}$C	degree Celsius
CDCl$_3$	deuterated chloroform
d	doublet (NMR)
dd	doublet of doublets (NMR)
dt	doublet of triplets (NMR)
Et$_2$O	ether
EtOAc	ethyl acetate
eguiv	equivalent(s)
GC	gas chromatography
g	gram(s)
Hz	hertz
h	hour(s)
[hmim][Br]	1-hexyl-3-methylimidazolium bromide (ionic liquid)
MB	mass balance
m.p.	melting point
mL	milliliter(s)
mM	millimolar
mmol	millimole
mg	milligram(s)
min	minute(s)

m	multiplet (NMR)
NMR	nuclear magnetic resonance
[omim][Br]	1-octyl-3-methylimidazolium bromide (ionic liquid)
ppm	part per million
q	quartet (NMR)
quant.	quantitative
s	singlet (NMR)
THF	tetrahydrofuran
t	triplet (NMR)

CHAPTER I

INTRODUCTION

1.1 Green industry

Green Industry means economies striving for a more sustainable pathway of growth, by undertaking green public investments and implementing public policy initiatives that encourage environmentally responsible private investments.

In recent years, environmental consciousness and considerations in chemical process design and simulation demand an effort extending far beyond the capability of existing process simulators to model processes with environmental control options. Green Industry promotes sustainable patterns of production and consumption. Patterns are resource and energy efficient, low-carbon and low waste, non-polluting and safe, and which produce products that are responsibly managed throughout their lifecycle. The Green Industry agenda covers the greening of industries, under which all industries continuously improve their resource productivity and environmental performance. It also aims to create green industries, that deliver environmental goods and services in an industrial manner, including, for example, waste management and recycling services, renewable energy technologies, and environmental analytical and advisory services. The greening of industries has become a core determinant of economic competitiveness and sustainable growth. Since resource inputs represent an important production cost for industries, improving efficiency gives industries a competitive advantage. The greening of industries also plays a role in poverty alleviation, through promoting energy security, health and safety, jobs, and reducing costs through increased productivity

The synthetic chemists, those who make chemicals and whose activities drive chemical processes, to become intimately involved in making the manufacture, use, and ultimate disposal of chemicals as environmentally friendly as possible. Before environmental and health and safety issues gained their current prominence, the economic aspects of chemical manufacture and distribution were relatively simple and

straightforward. The economic factors involved included costs of feedstock, energy requirements, and marketability of product. Now, however, costs must include those arising from regulatory compliance, liability, end-of-pipe waste treatment, and costs of waste disposal. By eliminating or greatly reducing the use of toxic or hazardous feed stocks and catalysts and the generation of dangerous intermediates and byproducts, green chemistry eliminates or greatly reduces the additional costs that have come to be associated with meeting environmental and safety requirements of conventional chemical manufacture.

1.2 Ionic liquids

One of twelve principles of green chemistry is the use of auxiliary substances such as solvents and separation agents should be made unnecessary and if used should be innocuous [1]. The toxic and hazardous properties of many solvents particularly chlorinated hydrocarbons pose crucial environmental concerns such as atmospheric emissions and contamination of water effluents. It is recognized that the use of nonconventional solvents as alternatives for environmentally unfriendly traditional solvents can reduce waste solvent production and hence reduce the negative impact on environment to a great extent [2] . The most prevalent of these new solvent systems includes, but not exclusively, water, supercritical fluids (like supercritical CO_2), ionic liquids, solventless processes, and fluorous techniques [3].

An ionic liquid (IL) is a salt in the liquid state containing both positive and negative charges. The charges on the ions in such compounds are much less concentrated than in simple inorganic compounds like NaCl. Ionic liquids are salts comprising organic cations (imidazolium, ammonium, pyrrolidinium, *etc.*) associated with inorganic anions (Cl^-, $AlCl_4^-$, PF_6^-, BF_4^-, NTf_2^-, DCA^-, *etc.*) or organic anions (CH_3COO^-, $CH_3SO_3^-$, *etc.*) which are liquid around room temperature. The characteristics of ionic liquid were high boiling point, non-volatility, viscous, easy separation, alternative solvent and reusability.

As solvents, ionic liquids have found applications in a number of reactions [4-6]. Dupont *et al.* extensively reviewed the application of ionic liquids as catalytic phase in various organometallic reactions [7]. Catalytic applications of metal nanoparticles have been explored in ionic liquid media by Migowski and Dupont [8, 9].

Besides the use of ionic liquids as alternate solvents, lately further work has led to the progress in designing functional ionic liquids also referred to as "task specific ionic liquids" (TSIL). The term "task specific ionic liquids" or "functionalized ionic liquids" actually indicates an attempt to capitalize on the potential "design" capacity of ionic liquids and make them true working systems rather than just reaction media.

There has been a lot of interest in the application of ionic liquids to green chemistry such as oxidation, hydrogenation, condensation, Micheal addition, Heck reaction, Suzuki coupling and the important reaction in industry is rearrangement of epoxides which provide aldehyde or ketone.

1.3 Literature review on the rearrangement of epoxides.

Epoxides are one of the most useful and versatile intermediates that serve as prominent building block in organic synthesis [3]. Not only are these compounds easily prepared from a variety of starting materials, but also the inherent polarity and strain of their three-membered ring makes them susceptible to the reactions with a large number of reagents. While epoxides are frequently employed as electrophiles in ring-opening nucleophilic-addition reactions, another common, useful and atom economical reaction is isomerization to form other functional groups. In the presence of a strong and bulky base, an epoxide may undergo a deprotonation-elimination sequence to form an allylic alcohol frequently with high stereoselectivity. Furthermore these epoxide-related transformations, the rearrangement of epoxides to carbonyl compounds have received considerable attention. The most well-known method to isomerize epoxides to carbonyl compounds involves the use of Lewis acids, generally *via* hydride, alkyl, or aryl 1,2-migration pathways.

The synthetically useful reactions of epoxide are indeed important in organic synthesis, pharmaceutical industries, perfumery and other chemical fields. For example: the uses of phenylacetaldehyde for preparing special types of rose perfumes, hydratropic aldehyde as type of hyacinth, lilac, and rose, homovanillin for resembles vanilla more closely than vanillin and acetophenone for raw material for the synthesis of some pharmaceuticals[10].

Phenylacetaldehyde   Hydratropic   Homovanillin
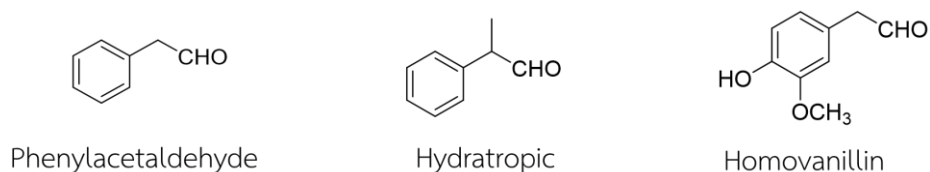
The catalysts for rearrangement of epoxide could be divided into two types: homogeneous and heterogeneous catalysts.

1.3.1 By homogeneous catalysts

In 1970, Rickborn and Gerkin reported that LiBr could be solubilized in benzene by the addition of equivalent amount of hexamethylphosphoramide (HMPA) or other phosphine oxide. The resultant complex was an efficient catalyst for the rearrangement of epoxides to aldehydes and/or ketones.
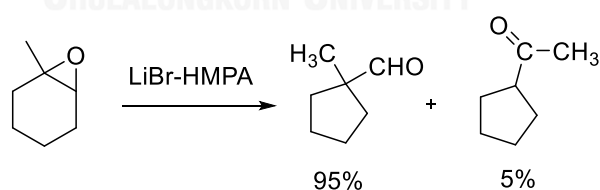
An interesting observation was made using 1-methylcyclohexene oxide as the substrate, LiBr catalyzed rearrangement of epoxides under very mild conditions and a degree of selectivity depending on the nature of the epoxides and the choice of lithium salt [11].

In addition, in 1994 Maruoka and colleagues continuously reported that methylaluminum *bis*(4-bromo-2,6-di-*tert*-butylphenoxide) (MABP) could be selectively

rearranged from trisubstituted epoxides to aldehydes, while SbF_5 was employable for selective rearrangement to ketones under mild conditions.
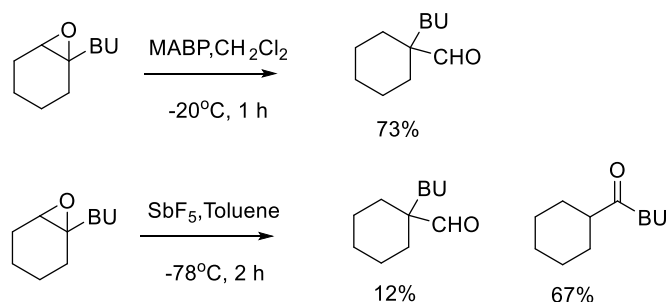
For the aldehyde synthesis, the use of a sterically hindered, oxygenophilic MABP would be the most suitable to affect the initial epoxide-cleavage followed by smooth alkyl transfer, in view of increasing steric repulsion between a bulky organoaluminum ligand and butyl group of epoxide [12].

In 1998, Ranu and Jana reported a simple and efficient procedure for the rearrangement of substituted epoxides catalyzed by $InCl_3$. Aryl-substituted epoxides could isomerize with complete regioselectivity to form a single carbonyl compound *via* cleavage of the benzylic C-O bond. 1-Aryl-, 1,1-diaryl- and 1,1-alkyl,aryl-substituted epoxides underwent rearrangement by exclusive hydride shift to give the respective aryl-substituted acetaldehydes as the only isolable compounds. While the rearrangement of tri- and tetra-substituted aryl epoxides selectively produced the corresponding ketones. The other notable advantages are fast reaction, mild reaction conditions, simplicity in operation, mild nature of $InCl_3$ in comparison to BF_3 and other Lewis acids and its compatibility with several acid sensitive functionalities [13].

R_1, R_2, R_3 = H, alkyl or phenyl
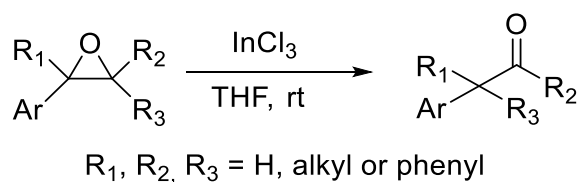
In 1998 Sankararaman and Nesakumar reported the highly chemo- and regioselective rearrangement of α,β-epoxy ketones to 1,3-dicarbonyl compounds in lithium perchlorate-diethyl ether (LPDE) medium by a 1,2-migration of the carbonyl group at ambient conditions [14].
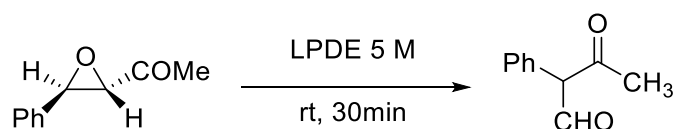
Recently, bismuth compounds have become attractive candidates in organic synthesis due to their low toxicity. In an earlier study, in 1999, Anderson and colleagues reported that aryl-substituted and aliphatic epoxides with a tertiary epoxide carbon underwent smooth rearrangement in the presence of 10-50 mol% $BiOClO_4 \cdot xH_2O$, to give carbonyl compounds. The rearrangement was regioselective with aryl-substituted epoxides while a single carbonyl compound arising from cleavage of benzylic C-O bond was formed [15].
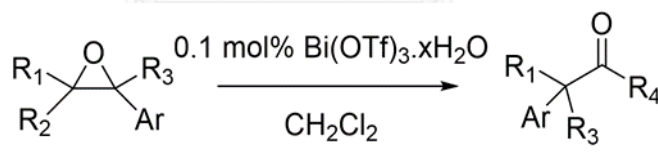
The rearrangement of both *cis-* and *trans-*stilbene oxides gave diphenylacetaldehyde as the only product in high yield. Nevertheless, the rearrangement of styrene oxide did not give a very pure product together with very low yield (15%) of phenylacetadehyde.

In addition, in 2001 Bhatia and colleagues reported that aryl-substituted epoxides underwent rearrangement smoothly in the presence of $Bi(OTf)_3 \cdot xH_2O$ (0.1 mol%) to carbonyl compounds [15].

In recent years, the promise of increased chemo-, regio-, and stereoselectivity available *via* transition metal catalysis has led investigators to study the interactions

of epoxides with transition metal complexes, and a number of interesting and useful isomerization reactions have been reported. Notably, epoxides activated by adjacent aryl, vinyl, silyl, or carbonyl substituents were isomerized to carbonyl compounds by complexes of Rh, Pd, Mo, Sm, Fe, *etc*. For instance in 1976, Alper and colleagues reported the use of the cheap metal carbonyl, molybdenum hexacarbonyl [Mo(CO)$_6$] for the rearrangement of epoxides to aldehydes in synthetically useful yields.

Treatment of the epoxides of *trans*-stilbene, styrene, **α**-methylstyrene and 1,1-diphenylethylene with a catalytic amount of Mo(CO)$_6$ in refluxing 1,2-DME afforded the rearranged aldehydes in 36-75% yield. A by-product of all reactions was the deoxygenated alkene having the same stereochemistry as the reactant epoxide. Small amounts of ketones were formed in several instances[16].
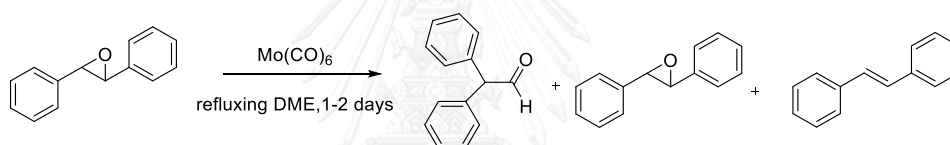
In 1997, Kulasegaram and Kulawiec reported isomerization of aryl-substituted epoxides bearing multiple methyl substituents on the epoxide ring in the presence of Pd(OAc)$_2$/PR$_3$ (R= *n*-Bu, Ph) to form the corresponding benzylic aldehyde or ketone, with complete regioselectivity for the carbonyl compound formed *via* cleavage of the benzylic C-O bond. In both reactions, the products were formed in high yield under mild conditions and depended on the substitution pattern of epoxides [17, 18].
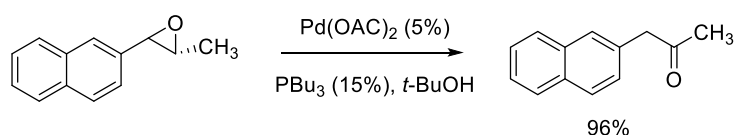
In 1999, Suda and colleagues reported the regioselective rearrangement of monoalkyl-substituted epoxides into aldehyes by Fe(tpp)OTf. The total yield and

regioselectivity of the products in the rearrangement were independent of the chain length of the epoxides used[19].
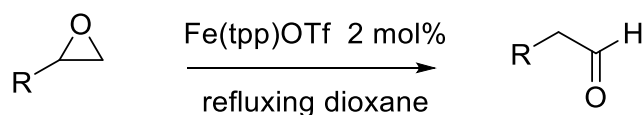
1.3.2 By heterogeneous catalysts

An important role in organic synthesis of heterogeneous catalysts was increasingly playing the same as homogeneous catalysts. For instance in 1988, Paparatto and Gregorio reported the use of H-ZSM-5 zeolite and silicalite as catalysts to convert styrene oxide to phenylacetaldehyde in almost quantitative yield. The reactions were carried out in a fixed bed catalytic reactor fed by a gaseous mixture of reagent and steam [20].

In 1999, Prakash and colleagues reported that Nafion-H, a perfluorinated resin sulfonic acid was found to be an efficient and simple catalyst for the isomerization of epoxides to ketones or aldehydes depending on the nature of the substituents on the epoxide carbons. The reaction was very straightforward which gave the products in high yield. Isoamylene oxide gave isopropyl methyl ketone and styrene oxide and its derivatives gave phenylacetaldehyde [21].
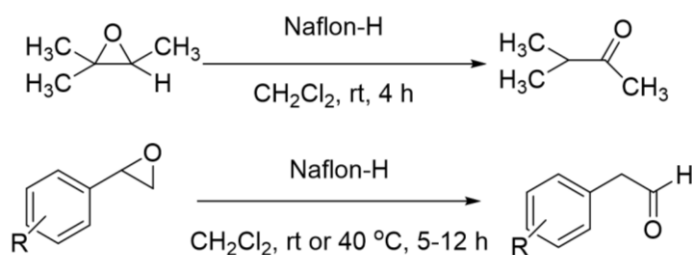
In 2005, Serrano and colleagues ceaselessly reported for the first time of the catalytic performance of Al-MCM-41 materials with different Si/Al molar ratios on the liquid-phase isophorone oxide rearrangement. The main rearrangement products were the keto aldehyde and the **α**-diketone. The best catalytic performance in terms of epoxide conversion was obtained for a catalyst with a molar Si/Al ratio around 40 due to the proper contribution of acid site concentration and pore size. However, irrespective of the aluminium content of the catalysts and the reaction temperature, the selectivity to the desired keto aldehyde was around 80% [22].
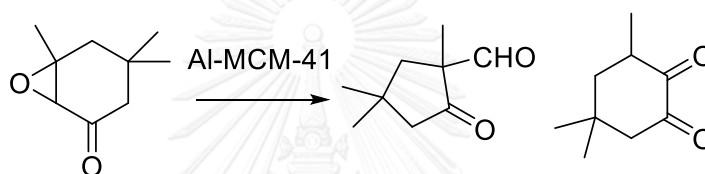
Recently, the use of zeolites for the isomerization of epoxide was of increasing interest. Mordenite is one of the zeolites catalogued as a strong acid zeolite. In 2005 Salla and colleagues reported the isomerization of styrene oxide to phenylacetaldehyde by fluorinated mordenites using microwave [23].

1.3.3 Nickel-catalyzed rearrangement in organic synthesis

From previous literatures, although several articles of homogeneous catalytic rearrangement reactions have been reported, only a few studies concerned with cheap, simple, selective and efficient rearrangement of epoxides by nickel catalysts have been discovered. For instance in 1986, Miyashita and colleagues reported that $NiBr_2(PPh_3)_2$ could catalyze ring opening isomerization of 1,2-epoxypropane to propionaldehyde under mild conditions, while $NiBr_2(PMe_2Ph)_2$ gave a mixture of acetone, propylene and aldehyde. PPh_3 was inactive for deoxygenation of epoxide under the same conditions. Regioselectivity for a C-O bond cleavage of epoxides was determined by the nature of the ligand coordinated to the metal center and thesubstitution pattern of epoxides [24].
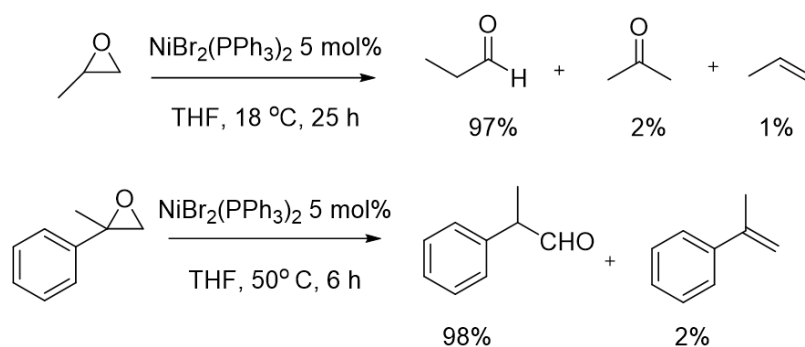
In 2006 Soponrattanapokin disclosed that the homogeneous system consisting of NiBr$_2\cdot$3H$_2$O was the most effective reagent for styrene oxide rearrangement. The quantitative yield of the corresponding phenylacetaldehyde was attained. Advantages of this method include low cost and commercially available catalyst, while the disadvantage is the recovery of catalyst, waste metal, and long reaction time.
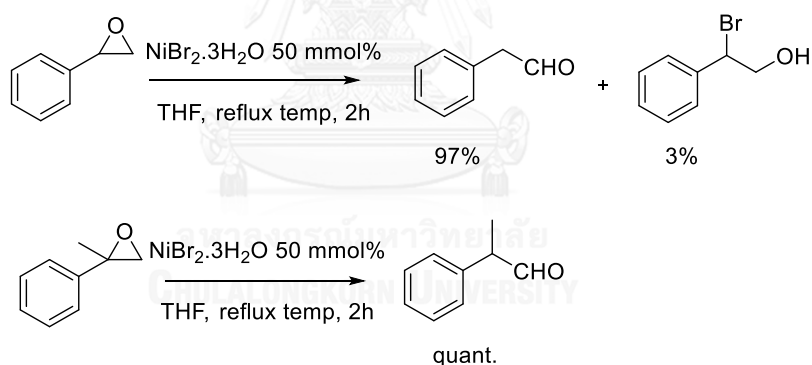
1.4 Literature review of ionic liquid.

Comparison the advantage and disadvantage between homogenous and heterogeneous catalysts, it was found that homogeneous catalysts exhibited higher-performance. However, major drawback is the difficulty of their recovery from the reaction. The advantages of heterogeneous catalysts were that they could be recycled easily, because the reactants and catalysts were in separated phases. Nevertheless, the efficiency of these catalysts generally lowers than homogeneous catalysts. The aim of this research is to combine the advantage of the homogenous catalyst (activity

and selectivity) with the facility of the heterogeneous systems to recycle the catalyst. Thus, the current design of chemical synthesis focuses on the green chemistry which minimizes the use of organic solvents. Ionic liquids are solvents composed of chemical compounds carrying ionic charges. The advantages of ionic liquids are green solvent, non-volatility, high boiling point, ease of separation, reusability and can be designed to suit the reaction.

In 2013, a library of ionic liquids was prepared by varying the cations and anions. Bi-functional acidic ionic liquids were prepared by direct combination of ionic liquids and $ZnCl_2$. Ionic liquids were investigated in Beckmann rearrangement which reacted acetophenone oxime to 95% yield of *N*-phenylacetamide and recyclable bi-functional acidic ionic liquid based protocol for Beckmann rearrangement [25].
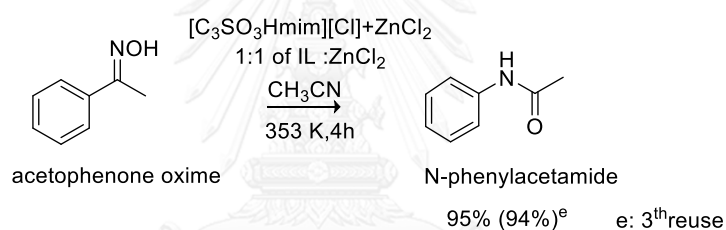
In the same year, Shaterian reported the synthesis of coumarin derivatives by ionic liquid catalyzed under solvent-free conditions. This reaction provided good to excellent yields under mild, ambient, and solvent-free conditions. The catalysts were environmentally benign and could be easily prepared, stored, and recovered 5 times without significant loss of activity [26].

Ionic liquids = [Hnmp][HSO$_4$], [NMP][HSO$_4$], [NMP][H2PO$_4$],(4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogensulfate and triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate.
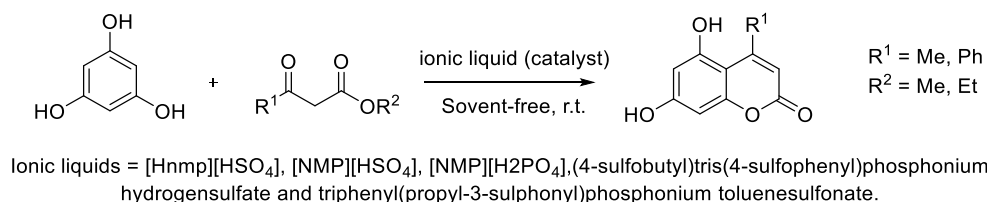
In 2014, Jamalian reported new methods and reagents for catalytic and regioselective conversion of 1,2-diarylepoxides to carbonyl compounds. Whereas the M(OTf)3/[BMIM][X] and[BMIM(SO3H)][OTf]/[BMIM][X] systems were highly efficient

methods for Lewis and Brønsted acids catalyzed epoxide ring openings, the [BMIM][PF6] by microwave requires no added catalyst. The recycling and reuse of the IL provided an added advantage for the described methods [27].

tran-stilbene oxide   2,2-diphenylacetaldehyde   1,2-diphenylethan-1-one
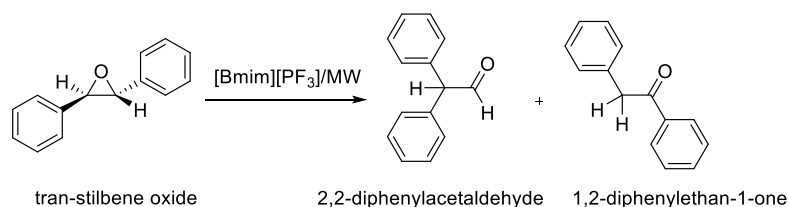
1.5 The goal of this research

The goal of this research could be summarized as

1. To develop the system comprising of transition metal salts for the rearrangement of aryl epoxides in ionic liquid.

2. To study the optimum conditions for rearrangement of aryl epoxides in ionic liquid by transition metal.

3. To apply the optimum conditions with other aryl epoxides and under microwave condition.

CHAPTER II

EXPERIMENTAL

2.1 General procedure

FT-IR spectra were recorded on a Nicolet Fourier transform infrared pectrophotometer model Impact 410. Solid samples were incorporated to potassium bromide to form a pellet. Liquid samples were dropped in sample holder.

The ^{1}H and ^{13}C NMR spectra were obtained in deuterated chloroform (CDCl$_3$) or deuterated dimethylsulfoxide (DMSO-d$_6$) on Varian and Bruker nuclear magnetic resonance spectrometer, model Mercury plus 400 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.

Chromatography: Thin layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel (Merck's, Kieselgel 60 PF254). Column chromatography was performed on silica gel (Merck's, Kieselgel 60 G) and alumina (Merck's, Aluminium oxide 90).

Gas chromatographic analysis was carried out on a Varian CP-3800 gas chromatograph instrument equipped with flame ionization detector with N$_2$ as a carrier gas. The column used for gas chromatograph was CP-Wax (30mx0.25mmx25μm) from VertiBond.

The X-ray diffraction measurements were made on a Rigaku XtaLAB P200 diffractometer using graphite monochromated Mo-K$_\alpha$ radiation. The crystal-to-detector distance was 30.17 mm.

The micro-reactor were made on Shikoku Instrumentation Company, Ltd. The 80% of microwave power and setting temperature at 90°C for 5 min was used for the reaction.

2.2 Chemical reagents

All solvents used in this research were purified prior to use by standard methodology except for those which were reagent grades. The reagents for synthesizing ionic liquids and all epoxides were purchased from Fluka and Aldrich chemical companies and were used without further purification.

2.3 Synthesis and characterization of ionic liquids

Ionic liquids used in this research consist of 1-butyl-3-methyl-imidazolium bromide ([bmim][Br]), 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF$_6$]), 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF$_4$]), 1-hexyl-3-methylimidazolium bromide ([hmim][Br]) and 1-octyl-3-methylimidazolium bromide ([omim][Br]).

[bmim][PF$_6$] and [bmim][BF$_4$] were purchased from Merck. Other ionic liquids were synthesized from reaction between 1-methylimidazole and 1-bromoalkane.

2.3.1 Synthesis and characterization of 1-alkyl-3-methylimidazolium bromide ([Xmim][Br]) [28]

The preparation of 1-alkyl-3-methylimidazolium bromide, [Xmim][Br], 1-methylimidazole 4 mL (50 mmol) was dissolved in toluene 6.5 mL. 1-Bromoalkane 50 mmol was slowly added and was stirred at 34 °C 48 h under nitrogen atmosphere. The reaction flask was immediately covered with aluminum foil. The obtained product was washed several times with EtOAc or Et$_2$O. Finally, ionic liquid was dried under vacuum.

[bmim][Br]: colorless liquid (9.9 g, 91% yield); ^{1}H NMR (CDCl$_3$) **δ** (ppm): 10.2 (s, 1H), 7.49 (t, *J* = 1.8 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 4.12 (t, *J* = 7.5 Hz, 2H), 3.90 (m, 3H), 1.60 (m, 2H), 1.12 (m, 2H) and 0.70 (t, *J* = 7.0 Hz, 3H).

[hmim][Br]: colorless liquid (12.3 g, 97% yield); ^{1}H NMR (CDCl$_3$) δ (ppm): 9.99 (s, 1H), 7.57 (t, *J* =1.7 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 4.30 (t, *J* = 7.4 Hz, 1H), 4.12 (m, 3H), 1.78 (m, 2H), 1.24 (m, 6H) and 0.67 (t, *J* = 6.9 Hz, 3H).

[omim][Br]: colorless liquid (12.5 g, 92% yield); ^{1}H NMR (CDCl$_3$) δ (ppm): 10.00 (s, 1H), 7.60 (t, *J* = 1.7 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 4.14 (t, *J* = 7.5 Hz, 2H), 4.00 (s, 3H), 1.73 (m, 2H), 1.21 (m, 10H) and 0.75 (t, *J* = 7.1 Hz, 3H).

2.4 Synthesis of authentic samples

2.4.1 Synthesis of 2-bromo-2-phenylethanol [12]

Styrene oxide 0.6 g (5 mmol) and Ni(NO$_3$)$_2$·6H$_2$O 0.73 g (2.5 mmol) was added in THF in the presence of LiBr 10 mmol (15 mL). The reaction was refluxed for 6 h. The mixture was extracted with Et$_2$O and H$_2$O. The organic layer was dried over anhydrous Na$_2$SO$_4$ and evaporated in vacuum. The residue was separated by silica gel column using hexane: EtOAc (8: 1). Finally, the solvent was removed by rotatory evaporator to yield the target product 1.86 g (93% yield).

2-Bromo-2-phenylethanol: yellow liquid; ^{1}H NMR (CDCl$_3$) δ (ppm): 7.36 (m, 5H), 4.95 (dd, *J* = 6.5, 7.2 Hz, 1H), 3.65 (dd, *J* = 7.2, 12.5 Hz, 1H), 3.12 (dd, *J* = 6.5, 12.4 Hz, 1H) and 2.22 (s, 1H).

2.4.2 Synthesis of phenylacetaldehyde [29]

Styrene oxide 0.24 g (2 mmol) was added into the mixture of 12 mg (10%wt) Fe-montmorillonite clay and 5 mL THF. The reaction was refluxed for 1 h. The clay was filtered out from the reaction mixture by vacuum suction. The filtrate was dried over anhydrous Na$_2$SO$_4$ and evaporated in vacuum. Finally, the solvent was removed by rotatory evaporator to yield the target product 0.23 g (95% yield).

Phenylacetaldehyde: yellow liquid; ^{1}H NMR (CDCl$_3$) δ (ppm): 9.75 (s, 1H), 7-8 (m, 5H) and 3.66 (s, 2H).

2.5 Synthesis of starting materials

2.5.1 Synthesis of α-methylstyrene oxide [30]

α-Methylstyrene 2.96 g (25 mmol) was added to a solution of *N*-bromosuccinimide (NBS) 4.45 g (25 mmol) in distilled water (40 mL) at room temperature. The reaction mixture was stirred vigorously at room temperature for 2 h. After this time, the product bromohydrin was separated from the aqueous layer which was extracted with Et_2O (2 x 20 mL). The extracts were combined with the bromohydrin, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude bromohydrin was then dissolved in NaOH (40 mL, 15% solution) and the mixture was stirred for 1 h at 60 °C. The epoxide product was separated from the aqueous layer by extraction with Et_2O (2 x 20 mL). The ether extracts were combined with the crude epoxide, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. Distillation of the crude mixture gave α-methylstyrene oxide 2.33 g (79% yield).

α-Methylstyrene oxide: colorless oil ^1H NMR (CDCl$_3$) δ (ppm): 7.30–7.14 (m, 5H), 2.90 (d, *J* = 5 Hz, 1H), 2.73 (d, *J* = 5 Hz, 1H) and 2.60 (s, 1H).

2.5.2 Synthesis of 1,1-diphenyloxirane

1,1-Diphenylethylene 0.9 g (5 mmol) was added to a solution of NBS 0.9 g (5 mmol) in distilled water (10 mL) at room temperature and the reaction mixture was stirred vigorously for 2 h. The product was separated from the aqueous layer by extraction with Et_2O (2 x 20 mL). The extracts were combined, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was then dissolved in NaOH solution (40 mL, 15% solution) and the mixture was stirred for 1 h at 60 °C. The epoxide product was separated from the aqueous layer by extraction with Et_2O (2 x 20 mL). The ether extracts were combined with the crude epoxide, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Distillation of the crude mixture gave the product 1,1-diphenyloxirane 0.77 g (85% yield).

1,1-Diphenyloxirane: yellow oil; ^{1}H NMR (CDCl$_3$) δ (ppm): 7.30–7.14 (10H, m), 3.20 (1H, d, *J* = 5 Hz).

2.5.3 Synthesis of *trans*-anethole oxide [31]

The mixture of 2.0 g (0.013 mmol) *trans*-anethole, 60 mL CH$_2$Cl$_2$ and 60 mL of 10% NaHCO$_3$ in ice-water bath was added a solution of 5.6 g of *m*-CPBA (85%, 0.028 mol) in 60 mL of CH$_2$Cl$_2$ over a period of 2.5 h. The CH$_2$Cl$_2$ layer was separated, washed with 10% Na$_2$CO$_3$ solution (3 x 25 mL) and saturated NaCl solution (25 mL), and dried over anhydrous Na$_2$SO$_4$. Finally, the solvent was removed by rotatory evaporator to yield the target product 1.86 g (93% yield).

trans-Anethole oxide: yellow liquid; ^{1}H NMR (CDCl$_3$) δ (ppm): 7.16-6.87 (m, 4H) , 3.75 (s, 3H), 3.50 (d, *J* = 2.1 Hz, 1H), 3.00 (dq, *J* = 5.2, 2.1 Hz, 1H) and 1.41 (d, *J* = 5.2 Hz, 3H).

2.6 The general procedure for the rearrangement of epoxides

2.6.1 Rearrangement of epoxides in THF

The solution of epoxide 1 mmol in THF (5 mL) containing a nickel reagent (1.0 mmol) in a round bottom flask was stirred at reflux temperature for 2 h. After the specific time or the reaction was completed (followed by TLC), 1 mL of the reaction mixture was taken and extracted with Et$_2$O. Finally, it was dried over anhydrous Na$_2$SO$_4$ and analyzed by GC with the addition of an exact amount of an appropriate internal standard.

2.6.2 Rearrangement of epoxides in ionic liquid

Epoxide (1 mmol) was added with nickel reagent (1 mmol) in ionic liquid (1 g). The reaction was stirred at 120 °C for 15 min. Then the reaction mixture was extracted with Et$_2$O (3 mL × 3 times). Finally, it was dried over anhydrous Na$_2$SO$_4$ and analyzed by GC with the addition of an exact amount of an appropriate internal standard.

2.7 Study on the optimum conditions for styrene oxide (1) rearrangement in ionic liquid

2.7.1 Effect of solvent and type of ionic liquid

The rearrangement of styrene oxide was carried out employing THF, [bmim][Br], [bmim][BF$_3$], [bmim][PF$_6$], [hmim][Br] and [omim][Br].

2.7.2 Effect of time and temperature

The rearrangement of styrene oxide was performed according to the general procedure mentioned earlier using NiBr$_2$·3H$_2$O as a reagent in ionic liquid, but different reaction temperatures (80, 100 and 120 °C) and reaction time (5, 15, 30, 60 and 120 min) were varied.

2.7.3 Effect of types of nickel reagents

The rearrangement of styrene oxide by NiBr$_2$·3H$_2$O was carried out in the same manner as previously described and changing the nickel reagent from NiCl$_2$·6H$_2$O, NiBr$_2$·3H$_2$O, NiI$_2$, Ni(acac)$_2$ or Ni(NO$_3$)$_2$·6H$_2$O as a reagent.

2.7.4 Effect of the ratio of NiBr$_2$·3H$_2$O: ionic liquid

The rearrangement of styrene oxide was carried out by different ratios of NiBr$_2$·3H$_2$O: ionic liquid (0:1, 1:0, 1:1, 1:0.5 and 1:2 mmol/mg).

2.8 Rearrangement of various selected epoxides

Selected epoxides including **α**-methylstyrene oxide, 1,1-diphenylethylene oxide, *trans*-stilbene oxide and anethole oxide were subjected to this developed rearrangement system by nickel reagents in ionic liquid. Other procedures were carried out as previously described.

2.9 General isolation procedure

After the reaction was completed (followed by TLC), the rearrangement 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. The product was characterized by ^{1}H NMR.

Phenylacetaldehyde: colorless oil; ^{1}H NMR (CDCl$_3$) **δ** (ppm): 9.75 (s, 1H), 7.39 (m, 5H) and 3.68 (s, 2H).

Acetophenone: colorless oil; ^{1}H NMR (CDCl$_3$) **δ** (ppm): 7.31 (5H, m) and 3.68 (s, 3H).

2,4-Diphenylbut-2-enal: colorless oil; ^{1}H NMR (CDCl$_3$) **δ** (ppm): 9.63 (s, 1H), 7.0-7.8 (m, 10H), 6.89 (t, *J* = 7.0 Hz, 1H) and 3.69 (d, *J* = 7.5 Hz, 2H).

Hydratropaldehyde: colorless liquid; ^{1}H NMR (CDCl$_3$) **δ** (ppm): 9.70 (s, 1H), 7.37 (m, 5H), 3.66 (q, *J* = 7.0 Hz, 1H) and 1.49 (d, *J* = 7.0 Hz, 3H).

2,2-Diphenylacetaldehyde: colorless liquid; ^{1}H NMR (CDCl$_3$) **δ** (ppm): 9.97 (d, *J* = 1.7 Hz, 1H), 7-8 (m, 10H) and 4.23 (d, *J* = 1.7 Hz, 1H).

1,2-Diphenylethanone: colorless liquid; ^{1}H NMR (CDCl$_3$) **δ** (ppm): 7.0-8.0 (m, 1H) and 4.23 (s, 1H).

4-Methoxyphenylacetone: deep yellow oil; ^{1}H NMR (CDCl$_3$) **δ** (ppm): 6.98 (m, 4H), 3.78 (s, 3H), 3.61 (s, 2H) and 2.12 (s, 3H).

1-(4-Methoxyphenyl)propan-1-one: deep yellow oil; ^{1}H NMR (CDCl$_3$) **δ** (ppm): 6.98 (m, 4H), 4.08 (s, *J* = 1.7 Hz, 3H), 3.71 (q, *J* = 7.2 Hz, 2H) and 0.99 (t, *J* = 7.2 Hz, 3H).

2.10 Reusing of NiBr$_2$·3H$_2$O in ionic liquid

The reaction containing nickel reagent in ionic liquid was evaporated to remove an extra solvent. Then epoxide was re-added into the reaction with recovered ionic liquid and was performed using the above mentioned method.

2.11 Determination of Lewis acidity of ionic liquid by IR spectroscopic probe [32]

Dried pyridine was used as a probe molecule for determination of Lewis acidities by monitoring the bands in the range of 1400–1700 cm^{-1}. Pyridine was added into the solution containing ionic liquid and nickel reagent by the ratio 1: 5. The FT-IR spectra were recorded with transmitting mode.

2.12 Rearrangement in [hmim][Br] under microwave irradiation synthesis

Epoxide (10 mmol) was added with nickel reagent (10 mmol) in ionic liquid (5 g) in autoclave. The reaction was stirred at 90 °C for 5 min at 300 rpm. Then the reaction mixture was extracted with Et$_2$O (5 mL × 3). Finally, it was dried over anhydrous Na$_2$SO$_4$ and analyzed by GC with the addition of an exact amount of an appropriate internal standard.

2.13 Characterization of the structure of nickel complex in ionic liquid by single crystal X-ray diffraction [33]

2.13.1 Synthesis of 1-ethyl-3-methylimidazolium bromide [emim][Br]

1-Methylimidazole 0.12 mmol and 1-bromoethane 0.12 mmol were refluxed for 24 h. The white solid was washed by cool hexane. Finally, ionic liquid was dried and characterized by ^{1}H NMR.

[emim][Br]: white solid; 1H NMR (CDCl3) δ (ppm): 10.30 (s, 1H), 7.55 (t, J = 1.8 Hz, 1H,), 7.53 (t, J = 7.5 Hz, 1H), 4.12 (m, 3H), 4.43 (t, J = 7.5 Hz, 2H) and 1.62 (m, 3H).

2.13.2 Reaction and recrystallization between [emim][Br] and NiBr$_2$.3H$_2$O

The mixture of [emim][Br] and NiBr$_2$ was refluxed in THF for 24 h yielding blue solid. After recrystallization by mixed solvents: MeOH, THF and CHCl$_3$, a blue prism crystal of C$_6$H$_{11}$Br$_4$N$_2$Ni was obtained. This crystal with approximate dimensions of 0.400 x 0.400 x 0.300 mm was mounted on a glass fiber and analyzed by X-Ray diffraction. The experimental details are presented in appendix.

CHAPTER III

RESULTS AND DISCUSSION

The rearrangement of epoxides mediated by transition metal salt generally produces aldehydes and ketones which are versatile intermediates in organic synthesis. Several protocols have consequently been developed and utilized for this purpose [34-37].

The current design of chemical synthesis focuses on the green chemistry which minimizes the use of solvent. Ionic liquid as green solvent is designed to suit the reaction. Thus the purpose of this research is to develop the catalytic system comprising of nickel reagent for the rearrangement of epoxides in imidazolium ionic liquids. Styrene oxide (**1**) was selected as a model substrate for reaction conditions optimization. The reaction conditions include type of ionic liquid, reaction temperature, reaction time, type of nickel reagent, and ratio of reagent : ionic liquid. Other substrates such as α-methylstyrene oxide (**6**), 1,1-diphenylethylene oxide (**7**), *trans*-stilbene oxide (**8**) and *trans*-anethole oxide (**9**) were chosen to examine the capability of the catalytic system and to explore the scope of this developed rearrangement system. Reuse study of nickel reagent in ionic liquid is important to develop catalytic system.

3.1 Characterization of synthesized ionic liquids

3.1.1 By ^{1}H NMR

Five ionic liquids used in this research consist of [bmim][Br], [bmim][PF$_6$], [bmim][BF$_4$], [hmim][Br], [omim][Br]. [bmim][PF$_6$] and [bmim][BF$_4$] were purchased from Merck. [Xmim][Br] (X= butyl, hexyl and octyl) were synthesized from the reaction between 1-methylimidazolium and selected 1-bromoalkane in toluene [28]. The attained ionic liquids were identified by ^{1}H NMR as shown in Figures 3.1-3.3 and Table 3.1.
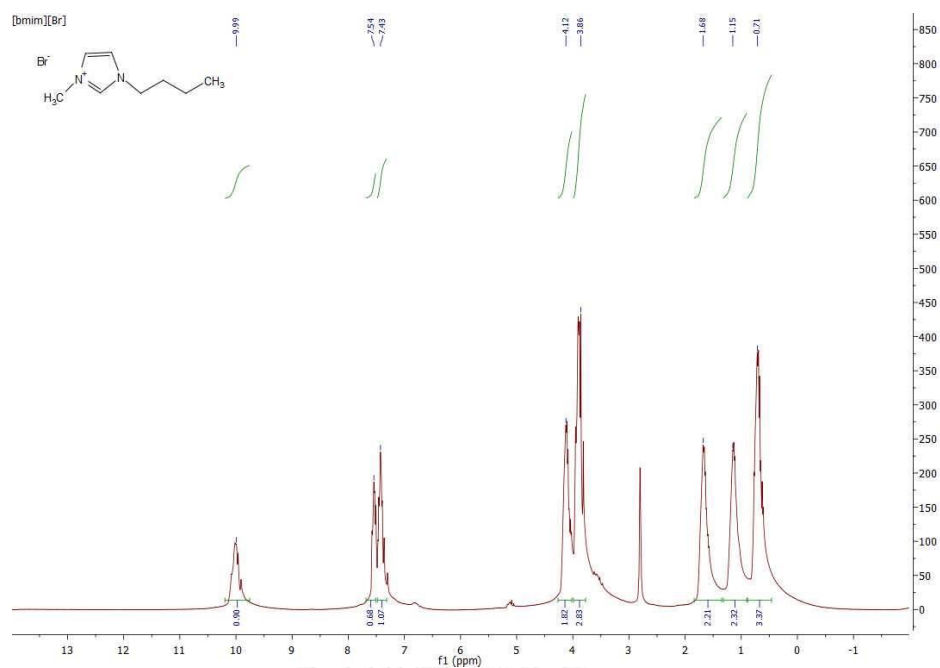
Figure 3.1 The ^{1}H NMR spectrum of [bmim][Br]
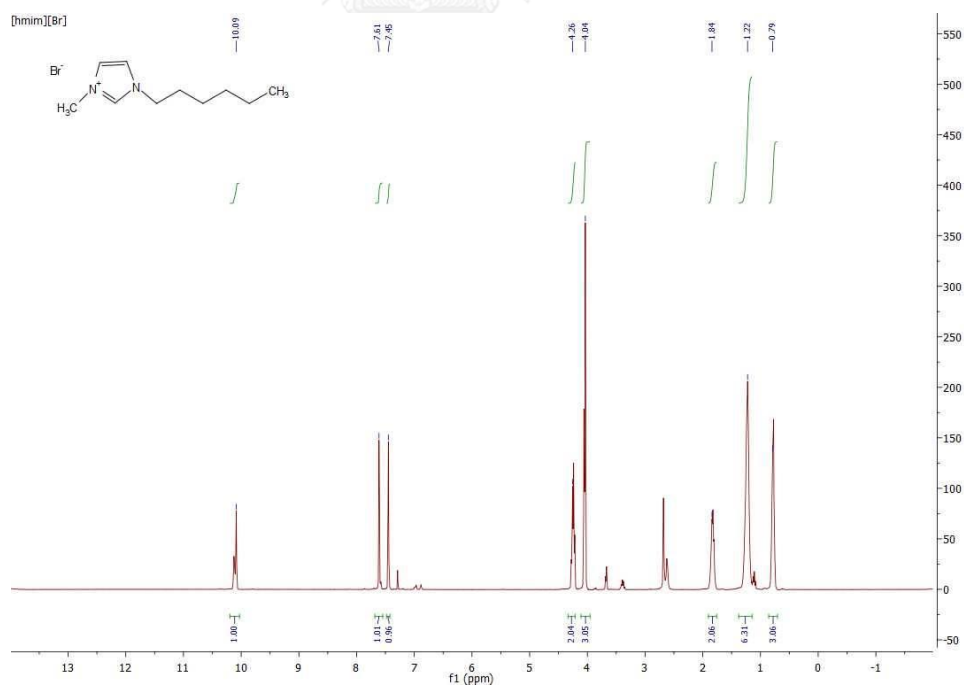
Figure 3.2 The ^{1}H NMR spectrum of [hmim][Br]
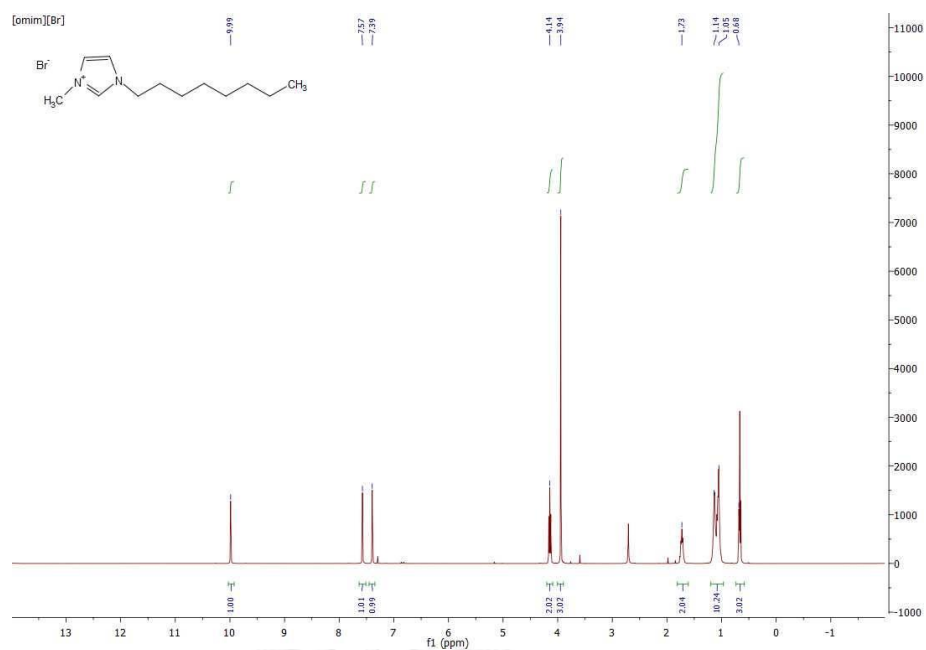
Figure 3.3 The ^{1}H NMR spectrum of [omim][Br]

Table 3.1 Chemical shift assignment of synthesized ionic liquids

Ionic liquids	Chemical shift (ppm)		
	Imidazole protons	methyl protons	alkyl protons
[bmim][Br] (CDCl₃)	10.2 (s, 1H), 7.49 (t, J = 1.8 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H)	3.90 (m, 3H)	4.12 (t, J = 7.5 Hz, 2H), 1.60 (m, 2H), 1.12 (m, 2H), 0.70 (t, J = 7.0 Hz, 3H)
[hmim][Br] (CDCl₃)	9.99 (s, 1H), 7.57 (t, J =1.7 Hz, 1H), 7.39 (t, J = 7.4 Hz, 1H)	4.12 (m, 3H)	4.30 (t, J = 7.4 Hz, 2H), 1.78 (m, 2H), 1.24 (m, 6H), 0.67 (t, J = 6.9 Hz, 3H).
[omim][Br] (CDCl₃)	10.00 (s, 1H), 7.60 (t, J = 1.7 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H,)	4.00 (s, 3H)	4.14 (t, J = 7.5 Hz, 2H), 1.73 (m, 2H), 1.21 (m, 10H), 0.75 (t, J = 7.1 Hz, 3H)

3.1.2 Characterization of the structure of nickel complex with ionic liquid

Single-crystal X-ray diffraction (XRD) is a non-destructive analytical technique which provides detailed information about the internal lattice of crystalline substances, including unit cell dimensions, bond-lengths and bond-angles. Directly related is single-crystal refinement, where the data generated from the X-ray analysis is interpreted and refined to obtain the crystal structure [38].

As a solid, [emim][Br] was chosen to substitute [hmim][Br]. Firstly, [emim][Br] was synthesized from the reaction between 1-methylimidazolium and bromoethane in THF. The white solid was washed by cold hexane and dried. The attained ionic liquid was identified by ^{1}H NMR.

The ^{1}H NMR of [emim][Br] (CDCl$_3$) spectrum (Figure 3.4) displays an imidazole proton at δ 10.30 (s, 1H), 7.55 (t, J = 1.8, 1H) and 7.53 (t, J = 7.5 Hz, 1H), methyl protons next to nitrogen at δ 4.12 (m, 3H) and ethyl protons at δ 4.43 (t, J = 7.5 Hz, 2H), 1.62 (m, 3H).
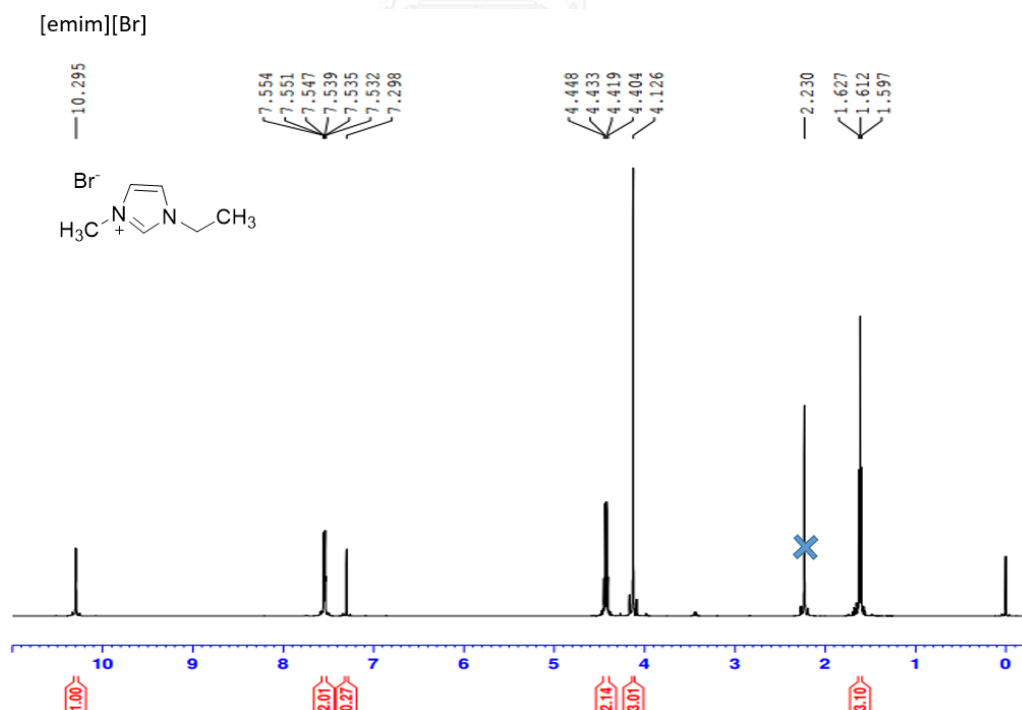
Figure 3.4 The ^{1}H NMR spectrum of [emim][Br]

Secondly, solid ionic liquid NiBr$_2$/[emim][Br] was synthesized from [emim][Br] and NiBr$_2$ in THF for 24 h. The product was obtained as blue crystal by recrystallization with mixed solvents: MeOH, THF and CHCl$_3$. To verify the structure of this nickel complex, the crystal was characterized by single crystal XRD.

The obtained crystal revealed a highly symmetrical tetragonal crystal lattice. NiBr$_4$ gave an average Ni-Br bond length of 2.391 Å and a Br-Ni-Br angle of 110.773° in distorted tetrahedral geometries. A model was constructed by placing between [emim]$^+$ and NiBr$_4$, Ni(IV) (Figure 3.5 A). The optimized geometry calculated for this configuration is shown in Figure 3.5 B. In the most stable geometry, Br$^-$ of NiBr$_4$ is nearly equidistant between the two nearly parallel [emim]$^+$ ions. The structure of NiBr$_4$/[emim] is stable with 18 electrons. This structure was consistent with the crystal packing in [Ph$_4$P] [FeCl$_4$] [39] and configuration of the [emim][AlCl$_4$] [33].

A   B
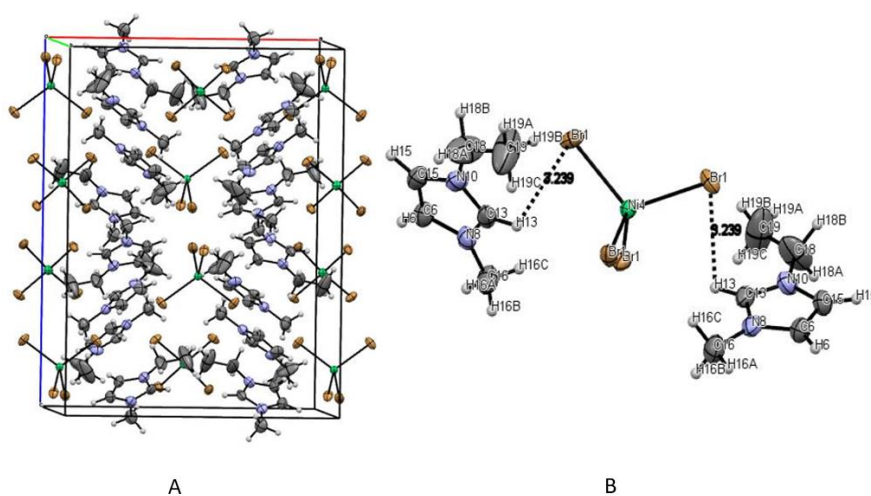
Figure 3.5 ORTEP diagram of the crystal structure A) Placing diagram between NiBr$_4$ and [emim]. B) ORTEP diagram of the crystal structure of NiBr$_4$/[emim]

3.2 Optimum conditions for styrene oxide (1) rearrangement

Generally, the rearrangement of epoxides towards aldehydes has been shown as an attractive strategy in cosmetics and fine chemicals [10]. Within the scope of this preliminary investigation, styrene oxide (**1**) was selected as a model substrate for optimization conditions. Several ionic liquids were chosen to evaluate their

compatibility with NiBr$_2$·3H$_2$O. Under this particular condition, the reaction provided phenylacetaldehyde (**2**) as a major product, while 2-bromo-2-phenylethanol (**3**), 2,4-diphenylbutyl-2-enal (**4**) and acetophenone (**5**) being minor.
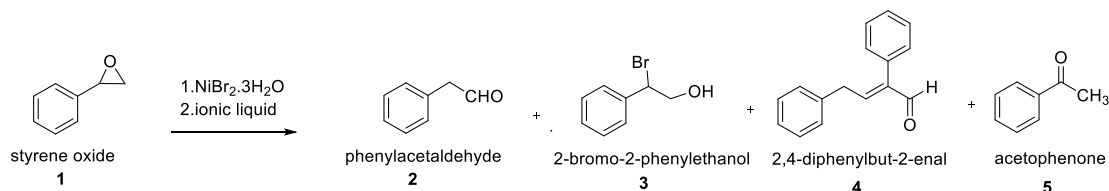
To verify the identity of the desired product, ^{1}H NMR was utilized. The ^{1}H NMR spectrum of phenylacetaldehyde (**2**) (Figure 3.6) revealed the aldehydic proton at δ 9.75 (s, 1H). The aromatic protons could be assigned at δ 7.31 (m, 5H), whereas those at benzylic position could be visualized at δ 3.68 (s, 2H).
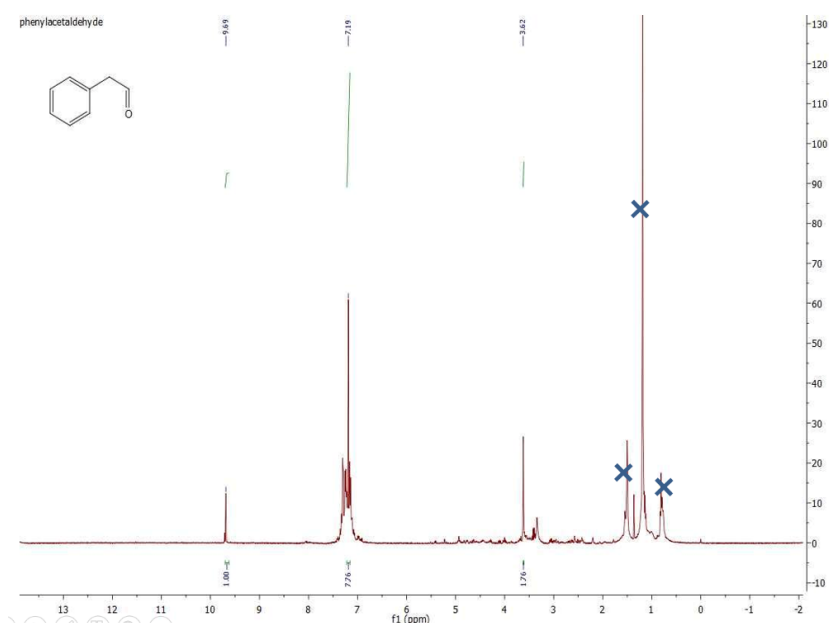
Figure 3.6 The ^{1}H NMR spectrum of phenylacetaldehyde (**2**)

3.2.1 Effect of ionic liquid on styrene oxide (1) rearrangement by NiBr$_2$•3H$_2$O

Ionic liquid always plays an important role to control the selectivity of the reaction. In this study, several ionic liquids were chosen to evaluate their compatibility with NiBr$_2$·3H$_2$O in the rearrangement of styrene oxide (**1**). The variation of ionic liquid

such as [bmim][Br], [bmim][BF$_4$], [bmim][PF$_6$], [hmim][Br] and [omim][Br] was carried out.

The polarity of common ionic liquids is similar to lower alcohols. There is a relationship between the chain length of alkyl substituents on the imidazolium cation and type of anion. For [bmim]$^+$ ionic liquids, the polarity decreased in the series of Br$^-$ > BF$_4^-$ > PF$_6^-$ [40]. Thus, the difference in polarity caused the difference in water solubility. Some ionic liquids are water soluble and some are not. PF$_6^-$ is generally water insoluble anion while Br$^-$ is generally water soluble anion. The higher polarity of Br$^-$ may assist the homogeneity of the reaction resulting in providing higher efficiency of the reaction (Figures 3.7).

a	b	c
NiBr$_2$·3H$_2$O is insoluble in [bmim][PF$_6$]	NiBr$_2$·3H$_2$O is slightly soluble in [bmim][BF$_4$]	NiBr$_2$·3H$_2$O is soluble in [bmim][Br]

Figure 3.7 NiBr$_2$.3H$_2$O in each ionic liquids; (a) NiBr$_2$.3H$_2$O is insoluble in [Bmim][PF$_6$], (b) NiBr$_2$.3H$_2$O is slightly soluble in [Bmim][BF$_4$], (c) NiBr$_2$.3H$_2$O is soluble in [hmim][Br].

The variation of type of ionic liquids on styrene oxide (**1**) rearrangement promoted by NiBr$_2$·3H$_2$O including [bmim][Br], [hmim][Br] and [omim][Br] was carried out and the results are presented in Table 3.2.

Table 3.2 Effects of type of ionic liquids on styrene oxide (**1**) rearrangement promoted by NiBr$_2$·3H$_2$O

Entry	Ionic liquid	% **1** (recovered)	Product (%)				Mass balance
			2	**3**	**4**	**5**	
1	THF	0	73	28	-	-	101
2	[bmim][Br]	0	54	1	31	13	99
3	[hmim][Br]	0	57	0	33	9	99
4	[omim][Br]	0	57	3	28	9	97

Reaction conditions: styrene oxide (**1**) (1 mmol), $NiBr_2 \cdot 3H_2O$ (1 mmol), ionic liquid (1 g), 120 ^{o}C for 2 h.

Comparing with a homogeneous system THF provided two products of phenylacetaldehyde (**2**) as a major product and 2-bromo-2-phenylethanol (**3**) (entry 1). Under the same reaction conditions, using ionic liquid, four products were analyzed suggesting by GC and ^{1}H NMR. Phenylacetaldehyde (**2**) occurred from the rearrangement of styrene oxide (**1**), while 2-bromo-2-phenylethanol (**3**) is a result of nucleophilic substitution of Br^{-} *via* S_N1. 2,4-Diphenylbutyl-2-enal (**4**) was derived from aldol condensation of phenylacetalphehyde (**2**). Nucleophilic substitution of Br^{-} *via* S_N2 and hydrogen migration provided acetophenone (**5**) (entries 2-4) (Scheme 3.1).
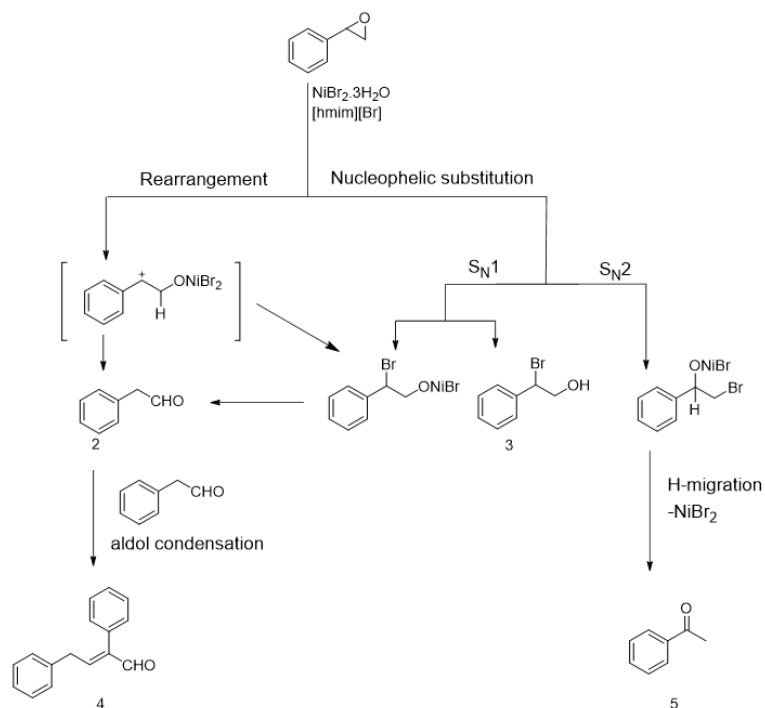
Scheme 3.1 Chart show products of styrene oxide (**1**) reacted with NiBr$_2$·3H$_2$O in [hmim][Br]

The effect of alkyl chain substituent of imidazolium cation was examined and found that three ionic liquids provided not different results (entries 2-4). Besides the ease to synthesize, this [hmim][Br] was liquid and could dissolve metal salt better than [bmim][Br]. Moreover, bromohexane could evaporate easier than bromooctane. Thus, under the experimental conditions studied, [hmim][Br] was selected for the next optimization experiment.

3.2.2 Effect of reaction time and temperature on styrene oxide (1) rearrangement by NiBr$_2$·3H$_2$O in [hmim][Br].

With the aim to maximize the yield of the desired aldehyde product, the variation of reaction time for styrene oxide (**1**) rearrangement by NiBr$_2$·3H$_2$O in [hmim][Br] was explored. The results are collected in Figure 3.8.
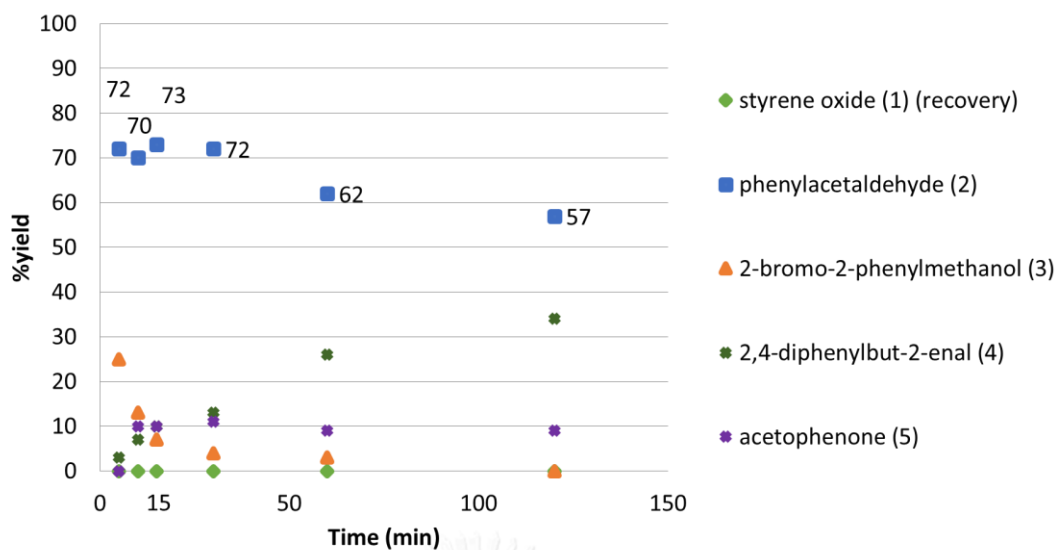
Figure 3.8 The variation of reaction time for the rearrangement of styrene oxide (**1**) promoted by NiBr$_2$·3H$_2$O in [hmim][Br].

The results in Figure 3.8 demonstrated that the rearrangement of styrene oxide (**1**) at 120°C by NiBr$_2$·3H$_2$O gave good yield of phenylacetaldehyde (**2**) within 30 min. However when increasing reaction time, the yield of phenylacetaldehyde (**2**) was decreased. That might be because the longer reaction time, the more 2,4-diphenylbut-2-enal (**4**) was produced. Within a short period of time of approximately 5 min, this reaction was completed quickly yielding approximately 70% of phenylacetaldehyde (**2**) and 25% of 2-bromo-2-phenylethanol (**3**). Therefore, the reaction time at 15 min was selected. The variation of reaction temperature on styrene oxide (**1**) rearrangement by NiBr$_2$·3H$_2$O was explored as presented in Figure 3.9.
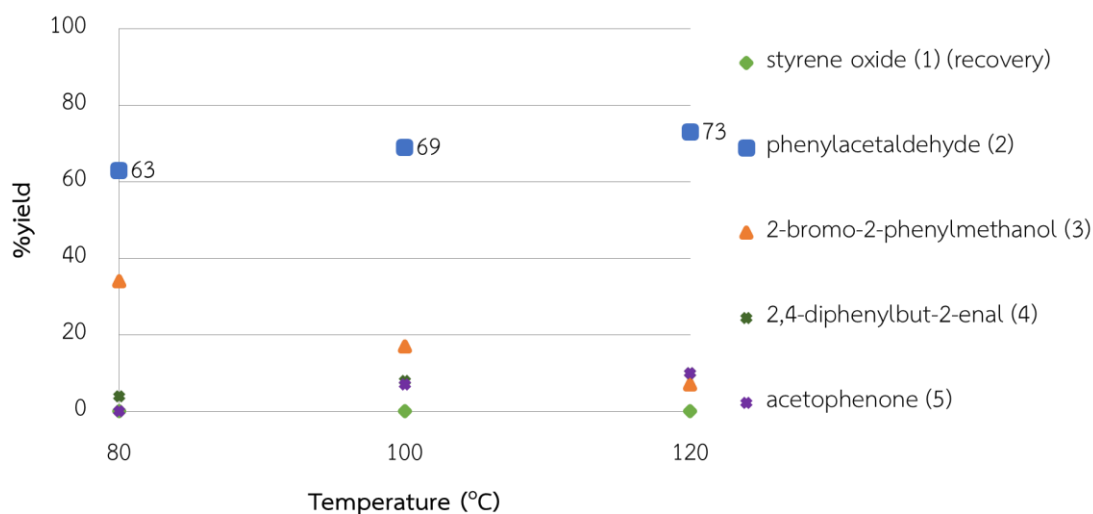
Figure 3.9 The variation of reaction temperature for the rearrangement of styrene oxide (1) mediated by NiBr$_2$·3H$_2$O in [hmim][Br].

The effect of the reaction temperature on styrene oxide (**1**) rearrangement by NiBr$_2$·3H$_2$O was explored. The results showed that the amount of the obtained phenylacetaldehyde (**2**) increased when temperature increased. As the temperature increased, the lower 2-bromo-2-phenylethanol was detected. This might be because the produced 2-bromo-2-phenylethanol (**3**) could be transformed to phenylacetaldehyde (**2**) at higher temperature [41]. However, over 120 ^{o}C, [hmim][Br] was decomposed by changing to gel. According to the above results, reaction time of 15 min at 120 ^{o}C was selected and kept constant as standard conditions for further investigation.

3.2.3 Effect of nickel reagents on styrene oxide (1) rearrangement in [hmim][Br]

In this research the effort was focused on screening of nickel reagents for the epoxide rearrangement. Most nickel compounds are readily available at low cost and fairly insensitive to small amount of water. The effects of nickel reagents, Ni(NO$_3$)$_2$·6H$_2$O, Ni(acac)$_2$ and nickel halide on styrene oxide (**1**) rearrangement are consequently examined. It was found that Ni(NO$_3$)$_2$·6H$_2$O and Ni(acac)$_2$ were insoluble in the media. So, these two nickel reagent were not further. While nickel halide could

be saluted in the media. The effects of nickel halide on styrene oxide (**1**) rearrangement are consequently examined and the results are presented in Table 3.3.

Table 3.3 Effects of type of nickel halide salts in [hmim][Br] on styrene oxide (**1**) rearrangement.
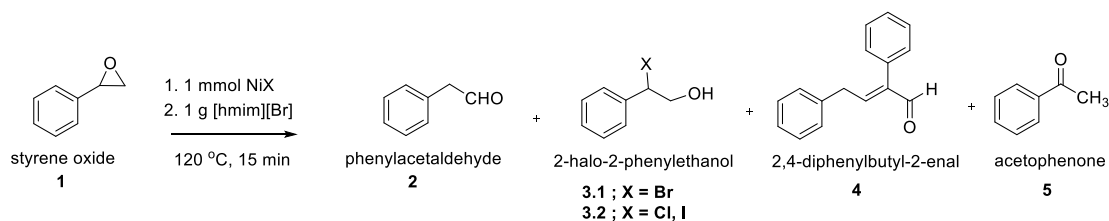
Entry	Nickel reagent	% **1** (recovered)	Product (%)				Mass balance
			2	**3.1, 3.2**	**4**	**5**	
1	none	100	-	-	-	-	100
2	$NiBr_2 \cdot 3H_2O$	0	73	7	10	10	100
3	$NiCl_2 \cdot 6H_2O$	0	70	7, 8	7	6	93
4	NiI_2	40	26	6, 9	5	4	90

Reaction conditions: styrene oxide (**1**) (1 mmol), nickel reagent (1 mmol), [hmim][Br] (1 g) at 120 ^{o}C for 15 min.

A control experiment clearly revealed that in the absence of the nickel salt, no reaction occurred (entry 1). Under the same reaction conditions, all attempts with nickel halide salts were interesting for further development. Nickel halide salts: $NiBr_2 \cdot 3H_2O$, $NiCl_2 \cdot 6H_2O$, and NiI_2, could assist the rearrangement of styrene oxide (**1**) to phenylacetaldehyde (**2**) (entries 2-4). Although $NiCl_2 \cdot 6H_2O$ provided phenylacetaldehyde (**2**) nearly the same amount as $NiBr_2 \cdot 3H_2O$, it also produced 2-cholo-2-phenylethanol (**3.2**). Moreover, 2-iodo-2-phenylethanol (**3.2**) was detected when using NiI_2. In addition, the presence of 2-bromo-2-phenylethanol (**3**) was derived from the attack of Br$^-$ of [hmim][Br]. This showed that 2-halo-2-phenylethanol could

occur from halide of nickel reagent and bromide of [hmim][Br]. For comparison with literature report, 1 mol% IrCl$_3$ provided 100% conversion of styrene oxide (**1**). However, this reaction might be used long reaction time around 2 h, 50 $^{\circ}$C [34]. The clear advantages of NiBr$_2$·3H$_2$O/[hmim][Br] system was faster reaction rate than IrCl$_3$. Moreover, NiBr$_2$·3H$_2$O was low cost and commercially available.

3.2.4 Effect of the ratio of NiBr$_2$·3H$_2$O: ionic liquid on styrene oxide (1) rearrangement in [hmim][Br]

With the aim to maximize the yield of the desired product, the ratio of NiBr$_2$·3H$_2$O: [hmim][Br] was studied and the results are collected in Figure 3.10.
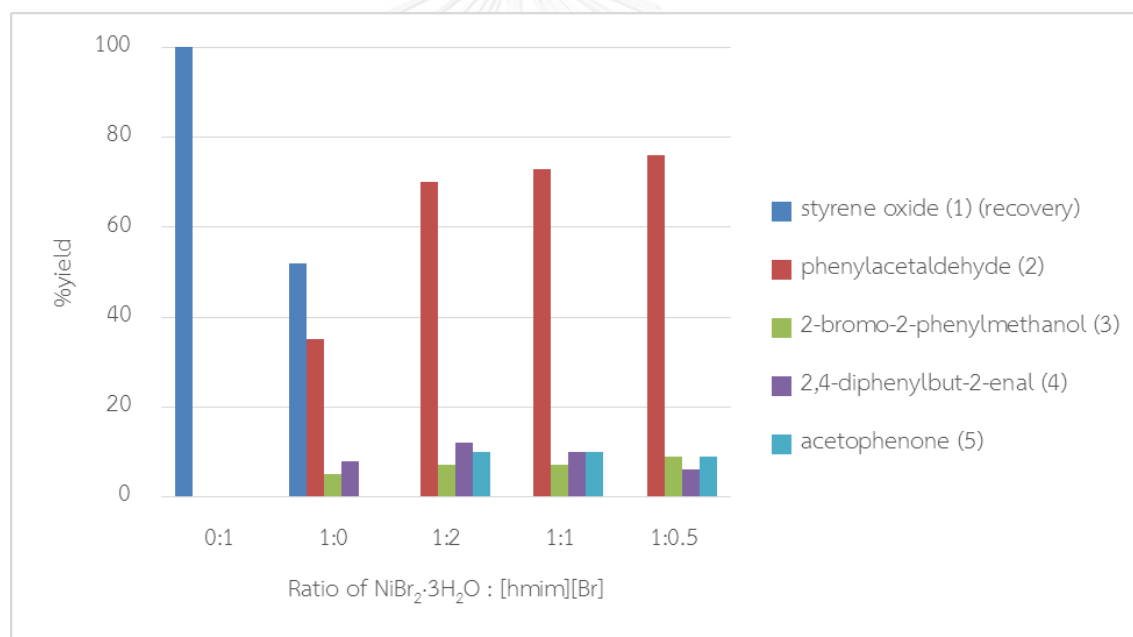
Figure 3.10 Ratio of NiBr$_2$·3H$_2$O: [hmim][Br] on the rearrangement on styrene oxide(**1**).

The reaction did not occurred in the absence of nickel salt. Without extra ionic liquid, low yield of phenylacetaldehyde (**2**) was obtained. With 1:0.5, 1:1, 1:2 of NiBr$_2$·3H$_2$O: [hmim][Br], the yield of phenylacetaldehyde (**2**) was not different. Thus, 1:0.5 of NiBr$_2$·3H$_2$O: [hmim][Br] was kept using throughout this study because ionic liquid was used in small amount.

From the outcome of variable factors studied above, it can be concluded that the optimum conditions for the rearrangement of styrene oxide (**1**) in the ionic liquid system are as follows: styrene oxide (**1**) 1 mmol as a substrate, $NiBr_2 \cdot 3H_2O$ 1.0 mmol as a reagent and [hmim][Br] 0.5 mg (ratio 1:0.5 of nickel reagent: [hmim][Br]) at 120 $^{\circ}$C for 15 min. The high yield of the corresponding phenylacetaldehyde (**2**) was attained.
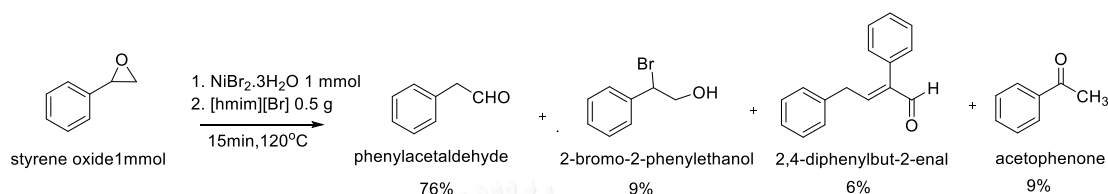
The optimum conditions of rearrangement of styrene oxide (**1**) mediated by $NiBr_2 \cdot 3H_2O$ in [hmim][Br].
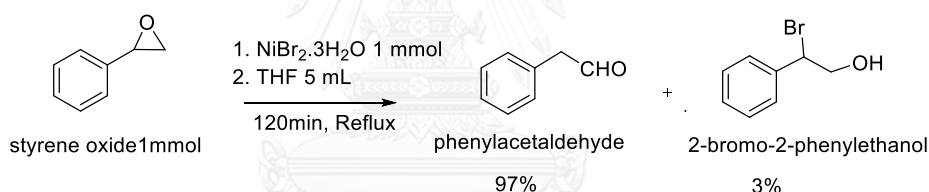
The optimum conditions of rearrangement of styrene oxide (**1**) mediated by $NiBr_2 \cdot 3H_2O$ in THF.

The comparative optimum condition between $NiBr_2 \cdot H_2O$/[hmim][Br] and $NiBr_2 \cdot H_2O$/THF found that $NiBr_2 \cdot H_2O$/THF provided good selectivity and high yield of the desired product. Nevertheless, a homogenous system used longer reaction time and the catalyst could not be reused. While ionic liquid system used short time and reusable. The rapid process utilizing ionic liquid system was believed to involve the more Lewis acidity of $NiBr_2 \cdot 3H_2O$/[hmim][Br] than that of $NiBr_2 \cdot 3H_2O$/THF. This was confirmed by determination of Lewis acidity by FT-IR spectroscopic probe.

Pyridine has been widely used as a probe for determination of the Lewis acidities by monitoring the band in the range of 1400–1450 cm^{-1} arising from its ring

vibration modes in FT-IR [32]. Normally, the band in plane of C-H wagging of pyridine appears around 1430 cm^{-1}. Nonetheless, when coordinating to Lewis acid site, this particular C-H band will shift to near 1450 cm^{-1} (Figure 3.11).
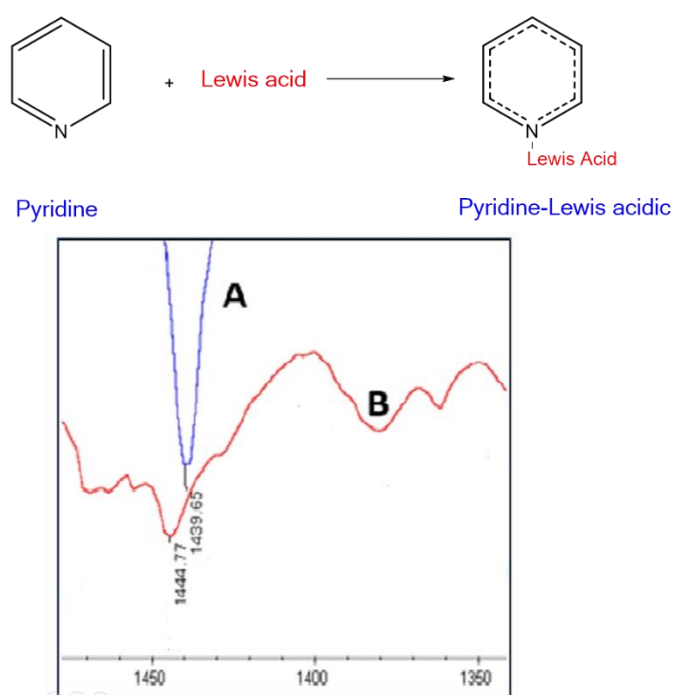
Figure 3.11 The FT-IR spectra of (A) pyridine+NiBr$_2$·3H$_2$O in THF;
(B) pyridine+NiBr$_2$·3H$_2$O in [hmim][Br].

Pyridine was added into nickel reagent. The FT-IR spectrum of the mixture of pyridine and NiBr$_2$·3H$_2$O in THF (Figure 3.11 (A)) shows a well resolved single band of C-H wagging of pyridine at 1439 cm^{-1}. As [hmim][Br] is a Lewis acid promoter [42], anion of ionic liquid might withdraw electrons from metal. Thus, the C-H wagging peck of pyridine with NiBr$_2$·3H$_2$O was shifted to 1445 cm^{-1} (Figure 3.11 (B)) which signified that ionic liquid influenced the acidity.

3.3 Study on the rearrangement of other aryl epoxides using NiBr$_2$·3H$_2$O in [hmim][Br].

After the reaction conditions were optimized using styrene oxide (**1**), the extended study on utilizing NiBr$_2$·3H$_2$O as a reagent in the rearrangement of other epoxides was scrutinized. Four aryl-substituted epoxides: **α**-methylstyrene oxide (**6**), 1,1-diphenylethylene oxide (**7**), *trans*-stilbene oxide (**8**) and *trans*-anethole oxide (**9**) were selected.

Aryl-substituted epoxides used in this study could not be obtained commercially. Therefore, they were prepared from the corresponding alkenes with oxone following standard procedures and purified by silica gel column. All aryl-substituted epoxides were verified their identities by ^{1}H NMR. Three prepared epoxides namely **α**-methylstyrene oxide (**6**), 1,1-diphenylethylene oxide (**7**) *trans*-anethole oxide (**9**) were selected as examples.

The ^{1}H NMR spectrum of **α**-methylstyrene oxide (6) (Figure 3.12) revealed the aromatic protons at **δ** 7.33 (m, 5H). Two terminal protons could be assigned at **δ** 2.98 (d, J = 5.4 Hz, 1H) and 2.81 (d, J = 5.4 Hz, 1H), whereas the significant singlet signal of methyl protons could be visualized at **δ** 1.72 (s, 3H).
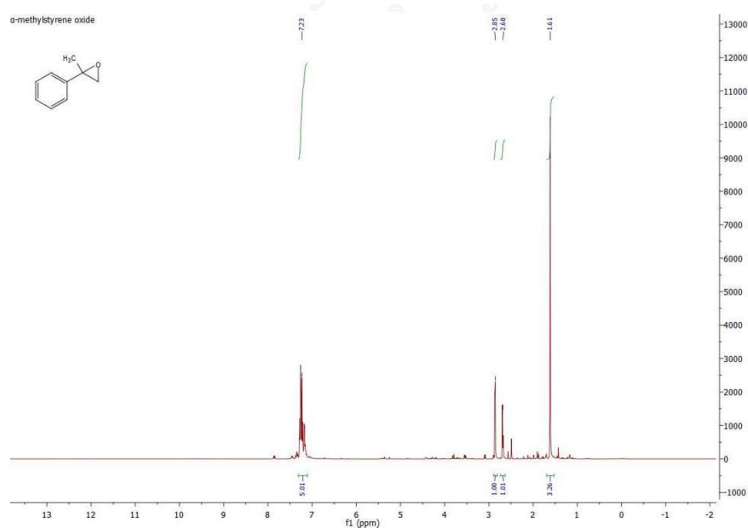
Figure 3.12 The ^{1}H NMR spectrum of **α**-methylstyrene oxide (**6**)

The ^{1}H NMR spectrum of 1,1-diphenylethylene oxide (**7**) (Figure 3.13) visualized the aromatic protons at δ 7.39 (m, 10H). The proton of epoxide ring was detected at δ 3.20 (s, 1H).
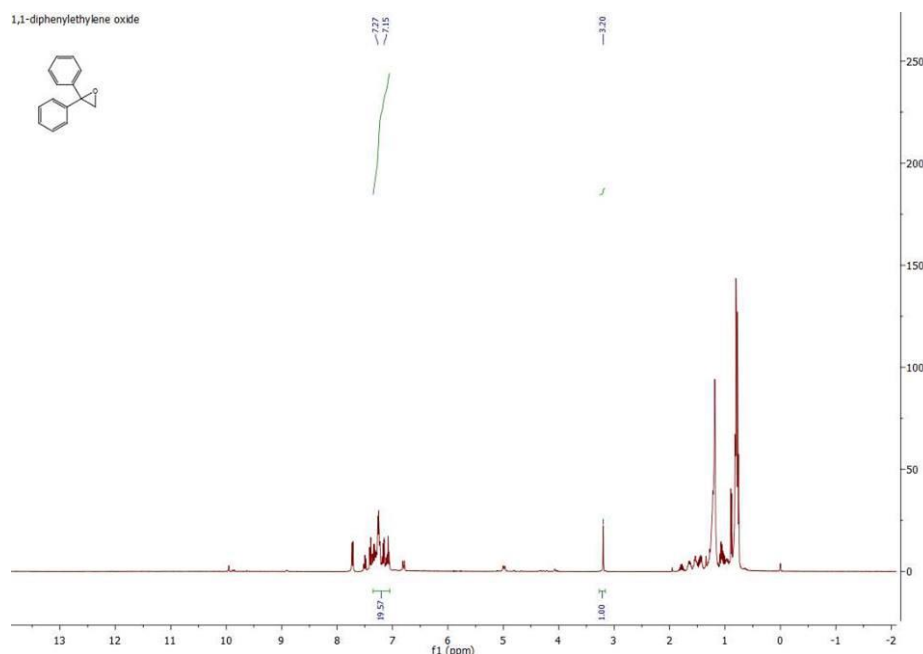
Figure 3.13 The ^{1}H NMR spectrum of 1,1-diphenylethylene oxide (**7**)

trans-Anethole oxide (**9**) synthesized by oxidation of *trans*-anethole was verified its identities by ^{1}H NMR. The ^{1}H NMR spectrum of *trans*-anethole oxide (**9**) (Figure 3.14) revealed the aromatic protons at δ 7.16, 6.87 (m, 4H). Three terminal protons of methoxy could be assigned at δ 3.80 (s, 3H). Hydrogen in epoxide ring 3.60 (d, *J* = 2.1 Hz, 1H), 3.05 (dq, *J* = 5.4, 2.3 Hz, 1H) whereas the significant singlet signal of methyl protons could be visualized at δ 1.43 (d, *J* = 5.6 Hz, 3H). The results of substrate scope was investigated as presented in Table 3.4.
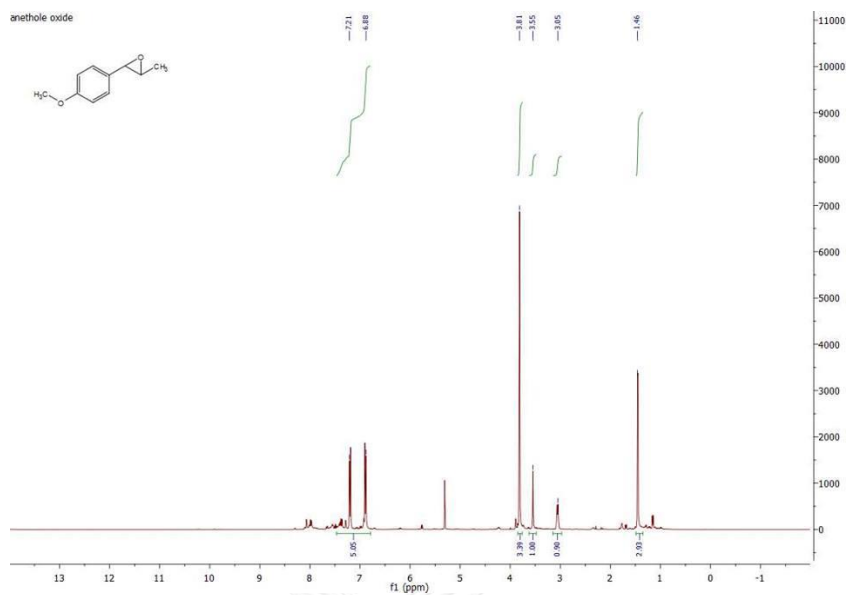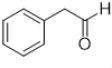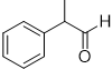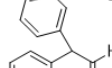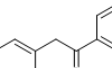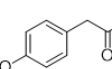
Figure 3.14 The ^{1}H NMR spectrum of trans-anethole oxide (**9**)

Table 3.4 The rearrangement of selected aryl epoxides using NiBr$_2$·3H$_2$O in [hmim][Br]

Entry	Substrate	Product	%Product	MB
1	**1**	**2**	76	107
2	**6**	**10**	70(29)[a]	99
3	**7**	**11**	73(18)[a]	91
4	**8**	**12**	67(24)[a](18)[b]	109
5	**9**	**13**	74(19)[a]	93

Reactions conditions: substrate (1 mmol), NiBr$_2$·3H$_2$O (1 mmol), [hmim][Br] (0.5 g) at 120 °C for 15 min.

    a) recovery of substrate

    b) % yield of 2,2-diphenylacetaldehyde (**11**)

Various aryl-substituted epoxides could provide the desired products in good yield with excellent selectivity (Table 3.4). Styrene oxide (**1**), **α**-methylstyrene oxide (**6**), 1,1-diphenylethylene oxide (**7**), *trans*-stilbene oxide (**8**) and *trans*-anethole oxide (**9**) (entries 1-5) underwent rearrangement to give the corresponding aldehydes or ketones.

The reaction of **α**-methylstyrene oxide (**6**) with NiBr$_2$·3H$_2$O in [hmim][Br] yielded hydratropaldehyde (**10**) as a main product 70%. 30% starting material was recovered.

The ^{1}H NMR spectrum of hydratropaldehyde (**10**) (Figure 3.15) signified an aldehyde proton at **δ** 9.70 (s, 1H) and five aromatic protons at **δ** 7.37 (m, 5H). The proton next to aromatic ring was observed at **δ** 3.66 (q, *J* = 7.0 Hz, 1H), while the methyl protons were detected at **δ** 1.49 (d, *J* = 7.0 Hz, 3H).
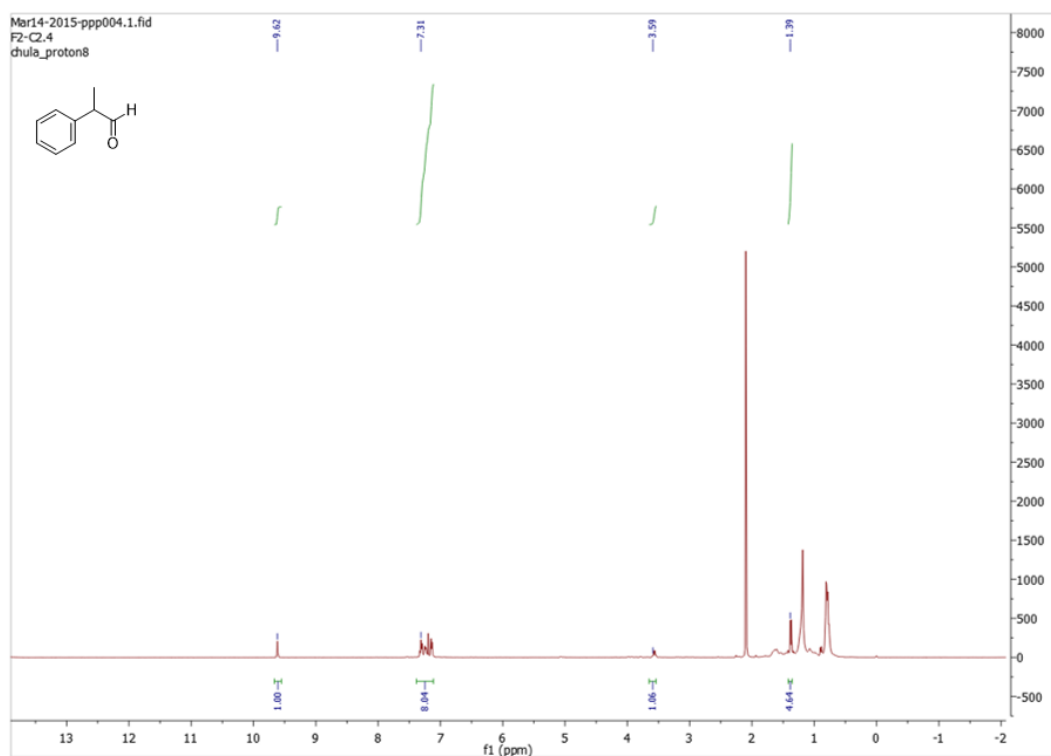
Figure 3.15 The ^{1}H NMR spectrum of hydratropaldehyde (**10**)

Treating 1,1-diphenylethylene oxide (**7**) with $NiBr_2·3H_2O$ in [hmim][Br], 2,2-diphenylacetaldehyde (**11**) 73%, occurred from ring opening of epoxide and hydrogen migration was achieved. Starting material was recovered 28%.

The ^{1}H NMR spectrum of 2,2-diphenylacetaldehyde (**11**) (Figure 3.16) showed the important aldehyde proton at δ 9.84 (s, 1H). The multiplet signal of aromatic protons could be observed at δ 7.25 (m, 4H), while the methine protons could be assigned at δ 4.95 (s, 1H).
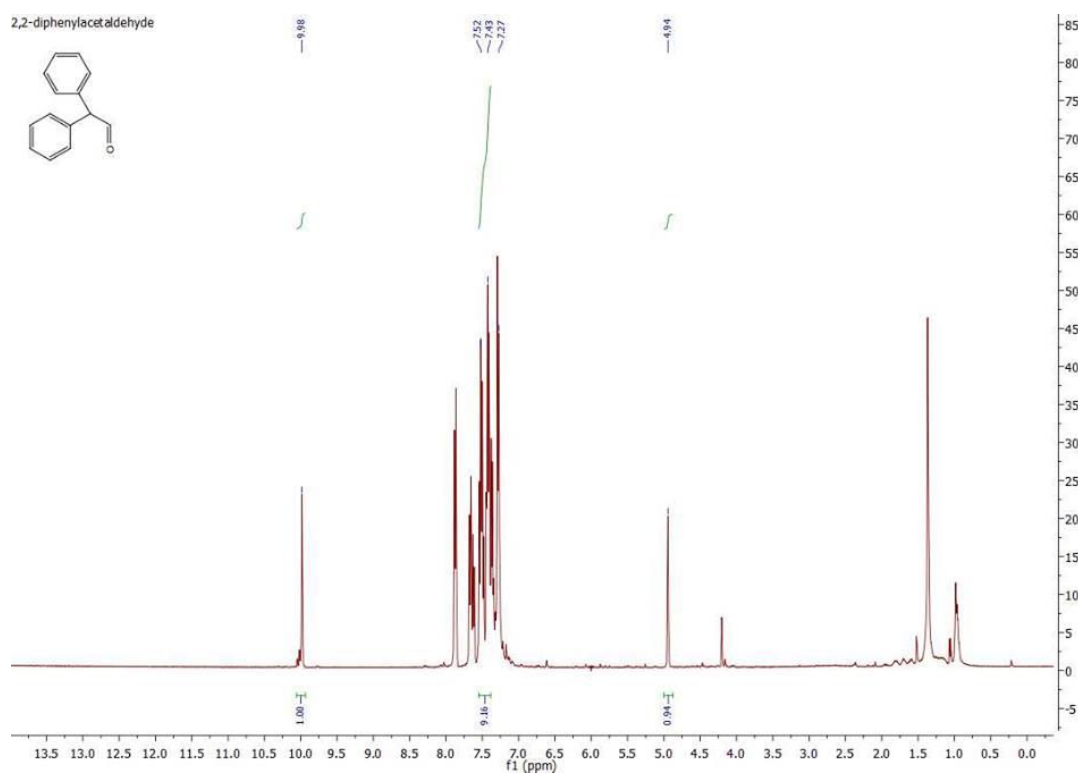
Figure 3.16 The ^{1}H NMR spectrum of 2,2-diphenylacetaldehyde (**11**)

To observe the effect of the substituent at β-position of aryl-substituted epoxides, *trans*-stilbene oxide (**8**) and *trans*-anethole oxide (**9**) were investigated (entries 4-5). The rearrangement of these two compounds (**8** and **9**) occurred selectively producing 1,2-diphenylethan-1-one (**12**) and 4-methoxyphenylacetone (**13**), respectively in excellent yield. These observed products were believed to derive from a competition between hydrogen and phenyl or methyl migration of *trans*-stilbene

oxide (**8**) or *trans*-anethole oxide (**9**). The hydrogen atom at β-position migrated in preference to phenyl or methyl group [43].

Two products: 1,2-diphenylethan-1-one (**12**) as a main product 67% and 2,2-diphenylacetaldehyde (**11**) as a minor product 18% were detected from the reaction of *trans*-stilbene oxide (**8**) with in [hmim][Br]. 24% of starting material was recovered.

The ^{1}H NMR spectrum of 1,2-diphenylethan-1-one (**12**) (Figure 3.17) visualized the two aromatic protons at δ 7.29 (m, 10H). The singlet signal of methylene protons could be observed at δ 4.30 (s, 2H).
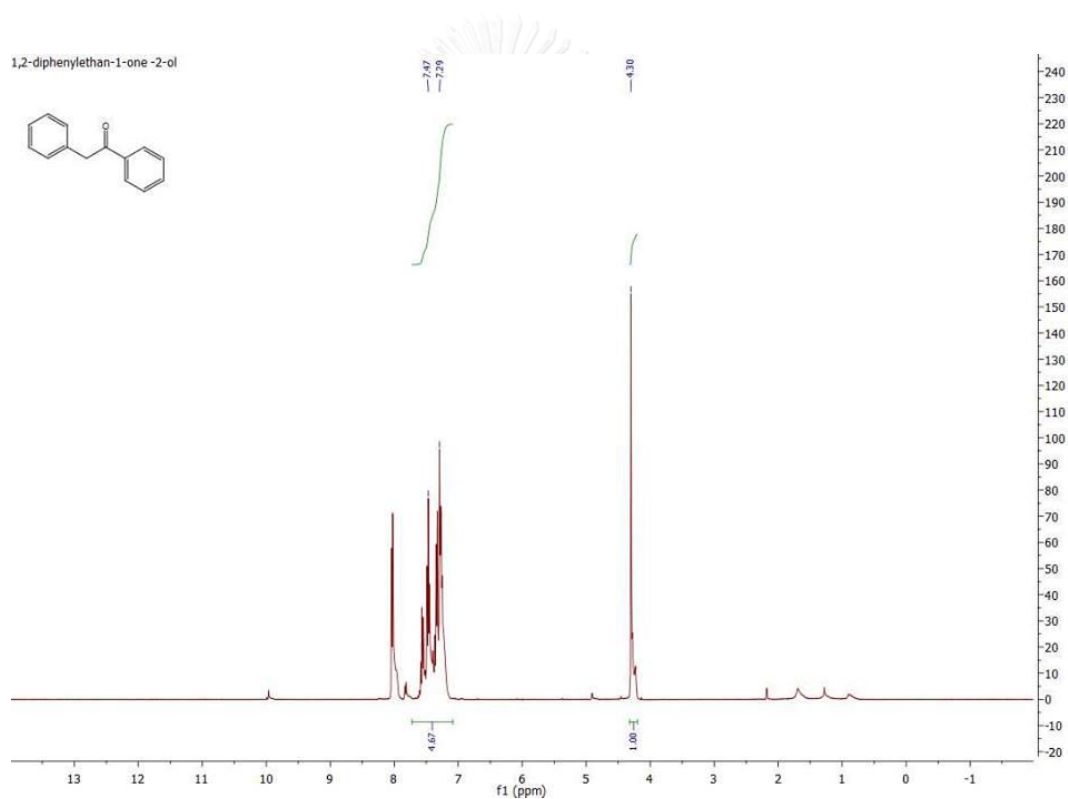
Figure 3.17 The ^{1}H NMR spectrum of 1,2-diphenylethan-1-one (**12**)

The ^{1}H NMR spectrum of 4-methoxyphenylacetone (**13**) (Figure 3.18) visualized the aromatic protons at δ 7.13 (d, *J* = 8.5 Hz 2H) and 6.88 (d, *J* = 8.5 Hz 2H). The singlet signal of methoxy protons could be observed at δ 3.78 (s, 3H), while the methylene protons could be seen at δ 3.61 (s, 2H). The methyl protons were detected at δ 2.12

(s, 3H). This observed product was believed to derive from a competition between hydrogen and methyl migration of *trans*-anethole oxide (**9**), hydrogen atom at **β**-position migrated in preference to methyl.
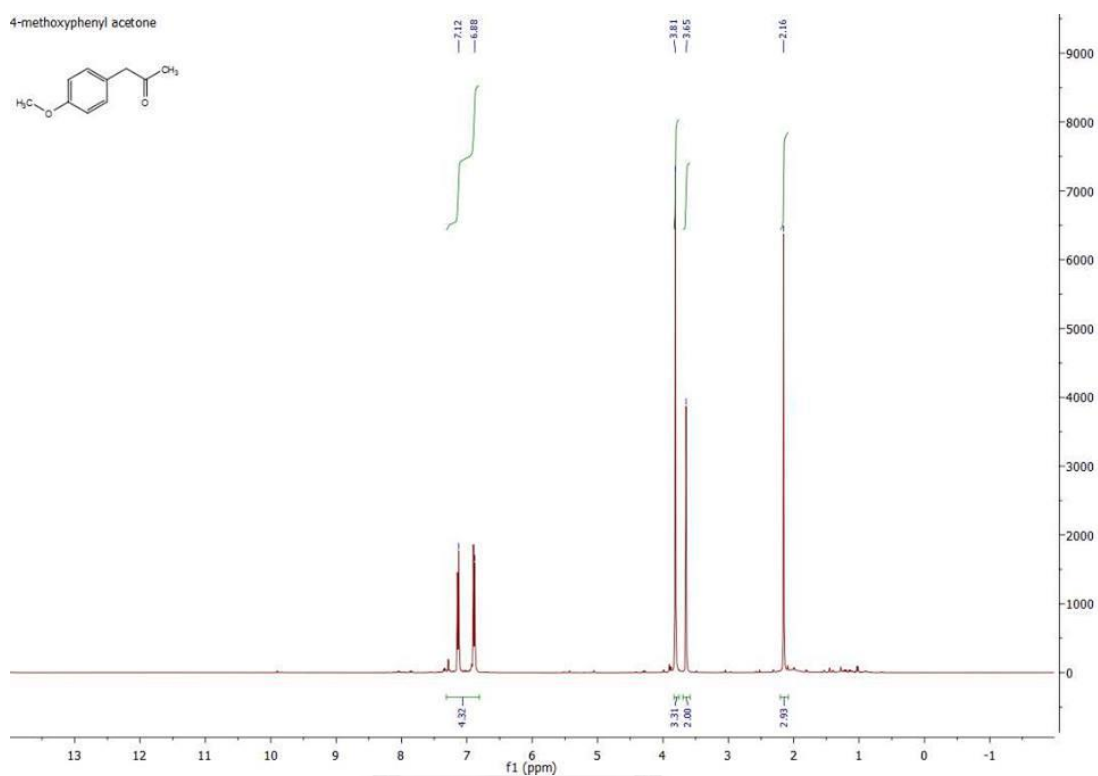
Figure 3.18 The ^{1}H NMR spectrum of 4-methoxyphenyl acetone (**13**)

3.4 Proposed mechanism for aryl epoxide rearrangement with NiBr$_2$·3H$_2$O in [hmim][Br]

Various aryl-substituted epoxides could be rearranged to give the desired products in good yield with excellent selectivity. Styrene oxide (**1**), **α**-methylstyrene oxide (**6**), 1,1-diphenylethylene oxide (**7**), *trans*-stilbene oxide (**8**) and *trans*-anethole oxide (**9**) underwent rearrangement to yield the corresponding aldehydes or ketones (Table 3.4 entries 1-5). A general mechanism of the rearrangement of aryl-substituted epoxides was believed to proceed *via* carbocation intermediate. Two types of products were generated depending upon the stable migration pathways of substituent and position of substituent.

1-Aryl-substituted epoxide as styrene oxide (**1**), 1,1-diaryl-substituted epoxide as 1,1-diphenylethylene oxide (**7**), and 1,1-alkyl,aryl-substituted epoxide as α-methylstyrene oxide (**6**) might be cleaved at benzylic C-O bond after being mediated by Lewis acid, and then exclusive by occurred *via* hydride shift. Using, THF provided aldehyde as a major product similar to the $NiBr_2 \cdot 3H_2O$/[hmim][Br] system (Table 3.4, entries 1-3).

The rearrangement of 1,2-disubstituted aryl epoxide such as *trans*-stilbene oxide (**8**) and *trans*-anethole oxide (**9**) in $NiBr_2 \cdot 3H_2O$/[hmim][Br] was greatly influenced by the nature of the substituent on aryl ring in competition between hydrogen and methyl or phenyl migration. The rearrangement of *trans*-stilbene oxide (**8**) with Lewis acid catalysts such as $InCl_3$ [13] and $IrCl_3$ [34] was reported to proceed *via* a phenyl migration to give 2,2-diphenylacetaldehyde (**11**) as a major product. However, $NiBr_2 \cdot 3H_2O$ in [hmim][Br] preferred hydride migration yielding 1,2-diphenylethan-1-one (**12**).

The presence of $NiBr_2 \cdot 3H_2O$/[himi][Br] resulted in different mechanistic pathway from homogeneous system as THF. Mechanistic studies involving Lewis acid catalyzed rearrangement of epoxides will be discussed in more details with styrene oxide (**1**) and *trans*-stilbene oxide (**8**).

3.4.1 Proposed mechanism on the rearrangement of styrene oxide (1)

The proposed mechanistic pathway of the rearrangement of styrene oxide (**1**) with $NiBr_2 \cdot 3H_2O$ in [hmim][Br] was presented in Figure 3.19. Firstly, the epoxide ring was dissociated by Lewis acid. The aromatic substituent was expected to stabilize a carbocation intermediate. The rearrangement of styrene oxide (**1**) by $NiBr_2 \cdot 3H_2O$ in [hmim][Br] provided four products as phenylacetaldehyde (**2**), 2-bromo-2-phenylethanol (**3**), 2,4-diphenylbutyl-2-enal (**4**) and acetophenone (**5**).
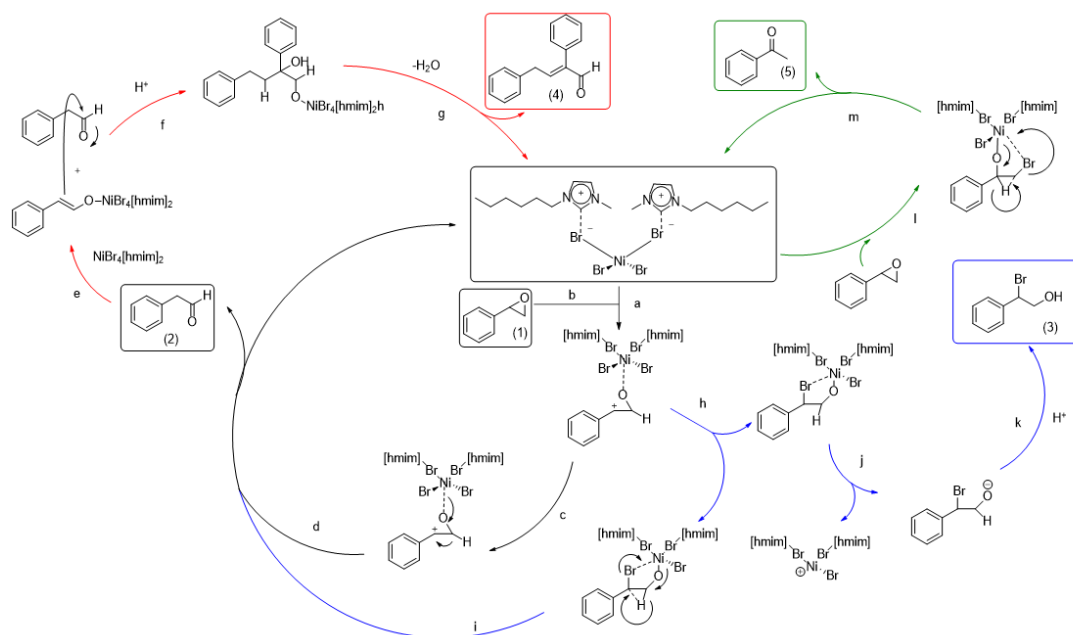
Figure 3.19 Proposed mechanistic pathway of the rearrangement of styrene oxide (**1**) using NiBr$_2$ .3H$_2$O in [hmim][Br].

Phenylacetaldehyde (**2**) should be occurred from ring opening mediated by NiBr$_2$·3H$_2$O (a), followed by hydrogen migration to carbocation of styrene oxide (**1**) (c, d). Moreover, carbocation could be attacked by bromide ion (h). Then, bromide elimination and hydrogen migration (i) provided phenylacetaldehyde (**2**). The production of 2,4-diphenylbutyl-2-enal (**4**) was derived from aldol condensation. Phenylacetaldehyde (**2**) could change to enol by Lewis acid (e) which then reacted with the carbonyl of phenylacetaldehyde (**2**) (f) yielding 2,4-diphenylbutyl-2-enal (**4**) (g). 2-Bromo-2-phenylethanol (**3**) should be formed *via* S$_N$1 by bromide ion (h). This product might be abstracted bromide ion from NiBr$_2$·3H$_2$O/[hmim][Br]. So NiBr$_2$·3H$_2$O/[hmim][Br] could not be recovered (j, k). The formation of acetophenone (**5**) was belived to occure *via* ring opening by S$_N$2 of bromide (l). Bromide elimination and hydrogen migration provided acetophenone (**5**) (m).

3.4.2 Proposed mechanism on the rearrangement of *trans*-stilbene oxide (8)

The comparative study between $NiBr_2 \cdot 3H_2O$/THF and $NiBr_2 \cdot 3H_2O$/[hmim][Br] on the rearrangement of this compound found that $NiBr_2 \cdot 3H_2O$/THF provided 52% of 2,2-diphenylacetaldehyde (**11**) as a sole product similar to $InCl_3$ and $IrCl_3$ systems. However, it was interesting to point out that in this research *trans*-stilbene oxide (**8**) with $NiBr_2 \cdot 3H_2O$/[hmim][Br] underwent a rearrangement to give a major product 65% as 1,2-diphenylethan-1-one (**12**), while 18% 2,2-diphenylacetaldehyde (**11**) was detected (Table 3.5).

Table 3.5 Comparative study on the rearrangement of *trans*-stilbene oxide (**8**) mediated by $NiBr_2 \cdot 3H_2O$ in different media.

1 mmol
trans-stilbene oxide
(**8**)

1. [hmim][Br] or THF
2. $NiBr_2.3H_2O$ 1 mmol
15 min, 120 °C

2,2-diphenylacetaldehyde
(**11**)

1,2-diphenylethan-1-one
(**12**)
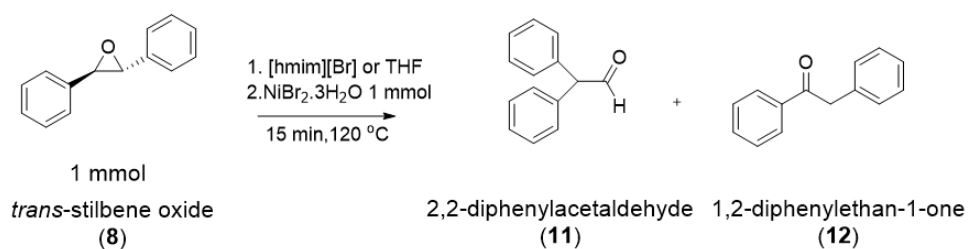
media	% **8** (recovery)	Product (%)		Mass balance
		11	**12**	
THF	49	52	0	100
[hmim][Br]	17	18	65	100

The products from both systems were different. Single crystal XRD displayed highly symmetrical tetragonal crystal lattice nickel complex in ionic liquid. Tetragonal of $NiBr_4$ was the most stable geometry. Br^- of $NiBr_4$ was nearly equidistant between the two nearly parallel [emim]$^+$ ions (Figure 3.5 B in 3.1.2). The oxidation number, steric effect, amount of bromide of $NiBr_4$ were more than $NiBr_2 \cdot 3H_2O$ in THF. In $NiBr_2 \cdot 3H_2O$/[hmim][Br] system, an epoxide ring was opened by the attacking of the bromine ion assisted by coordination of oxygen to Lewis acidic Ni(IV) (Figure 3.20, c). In the transition state, the bromide ion was almost completely dissociated, while the

proton was still close by possibly interacting with the carbon. This is a result in specially hydride migration product in ionic liquid system [44] (Figure 3.20, d). While $NiBr_2 \cdot 3H_2O$ in THF preferred Lewis acid pathway which phenyl could migrate to carbocation. Thus, the major product of *trans*-stilbene oxide (**8**) from both systems were different. The comparative rearrangement mechanistic pathway of *trans*-stilbene oxide (**8**) between $NiBr_2 \cdot 3H_2O$/THF and $NiBr_2 \cdot 3H_2O$/[hmim][Br] system is shown in Figure 3.20.
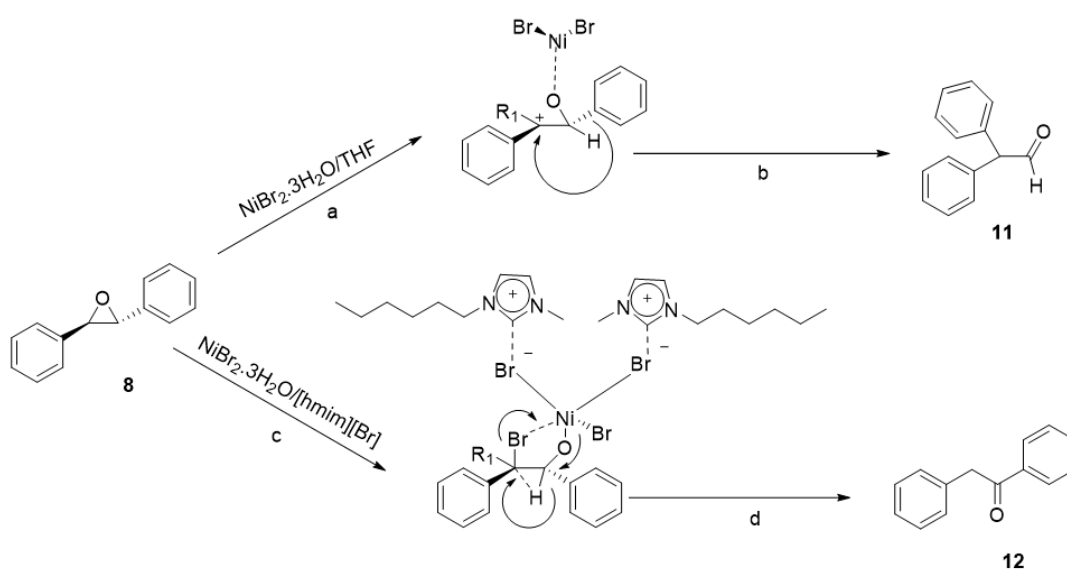
Figure 3.20 Comparative rearrangement mechanistic pathway of trans-stilbene oxide (**8**) between $NiBr_2 \cdot 3H_2O$/THF and $NiBr_2 \cdot 3H_2O$/[hmim][Br] system.

3.5 The effect of reusing of $NiBr_2 \cdot 3H_2O$ in ionic liquid.

In green organic synthesis, catalyst recovery is important. New reactants were recharged into the reaction flask containing recovered ionic liquid and the reaction was performed as previously descried. The study on reusing of nickel reagent in ionic liquid was conducted using styrene oxide (**1**) and α-methylstyrene oxide (**6**) as two models (Figure 3.21).
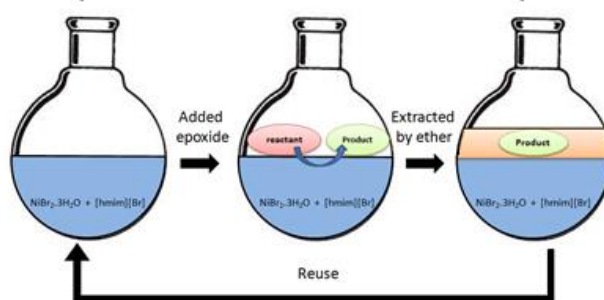
Figure 3.21 The rearrangement of epoxides by reused $NiBr_2 \cdot 3H_2O$/[hmim][Br].

3.5.1 Effect of reused $NiBr_2 \cdot 3H_2O$/[hmim][Br] on α-methyl-styrene oxide (6)

The synthetically useful reactions of epoxide are indeed important in organic synthesis, pharmaceutical industries, perfumery and other chemical fields. Hydratropadehyde was synthesized by the reaction of α-methylstyrene oxide (6) with $NiBr_2 \cdot 3H_2O$ in [hmim][Br]. The prospects for reusing ionic liquid was examined as presented in Figure 3.22.
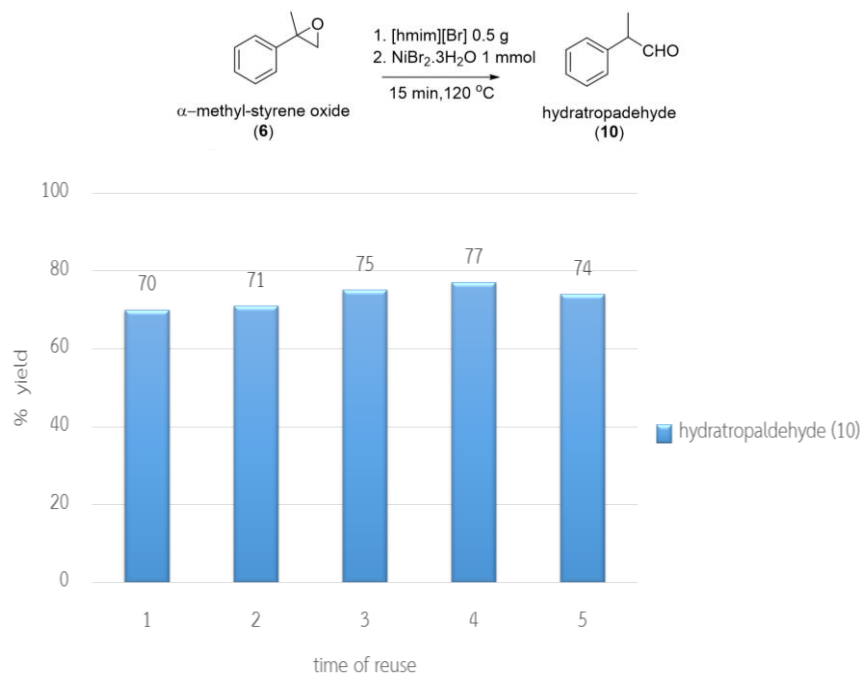
Figure 3.22 The rearrangement of α-methylstyrene oxide (6) mediated by reused $NiBr_2 \cdot 3H_2O$/[hmim][Br].

The activity of recovered [hmim][Br] was tested in subsequent runs for the rearrangement of **α**-methylstyrene oxide (**6**) without addition of fresh reagent for five runs. It was observed that this ionic liquid containing nickel salt displayed very good reusability without significant loss of their activity.

3.5.2 Effect of reused NiBr$_2$·3H$_2$O/[hmim][Br] on styrene oxide (1).

Phenylacetaldehyde (**2**) as rose perfume could be synthesized by the reaction of styrene oxide (**1**) and NiBr$_2$·3H$_2$O in [himi][Br] with 77% yield. The reusability of [hmim][Br] in the synthesis of phenylactaldehyde (**2**) from styrene oxide (**1**) was investigated as shown in Figure 3.23.
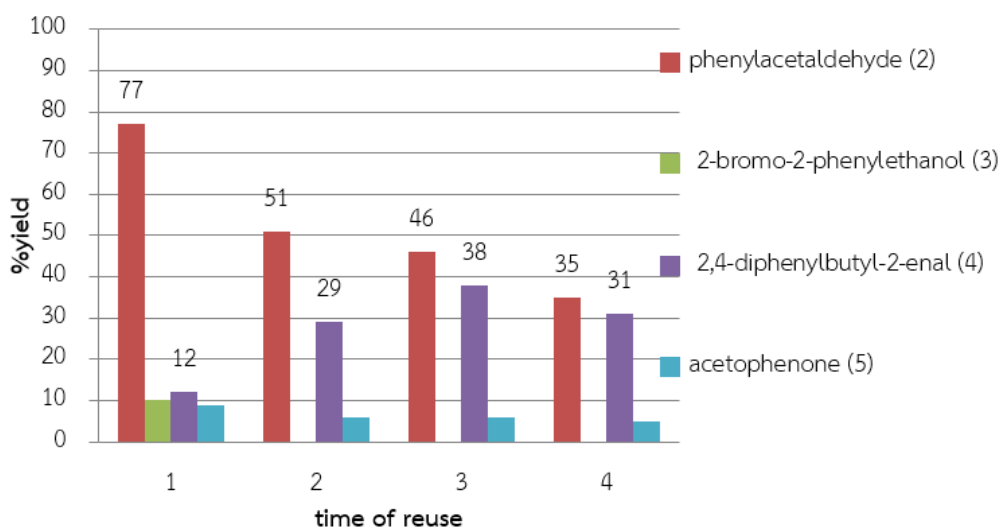
Figure 3 . 2 3 The rearrangement of styrene oxide (**1**) mediated by reused NiBr$_2$·3H$_2$O/[hmim][Br].

The results showed that NiBr$_2$·3H$_2$O/[hmim][Br] could not be reused based on the observation of the downward trend of phenylacetaldehyde (**2**) which was converted to 2,4-diphenylbutyl-2-enal (**4**). Moreover, 2-bromo-2-phenylethanol (**3**) was not detected in the second reuse. This might be possible that 2-bromo-2-

phenylethanol (**3**) could transform to 2,4-diphenylbutyl-2-enal (**4**). With independent experiment, 32% 2,4-diphenylbutyl-2-enal (**4**) was observed when 2-bromo-2-phenylethanol (**3**) was treated with phenylacetaldehyde (**2**).

The driving force for 2,4-diphenylbutyl-2-enal (**4**) production might be derived from the increment of the acidity of $NiBr_2 \cdot 3H_2O$/[hmim][Br]. The Lewis acidity of before and after reused nickel complex/ionic liquid was examined by FT-IR as presented in Figure 3.24.
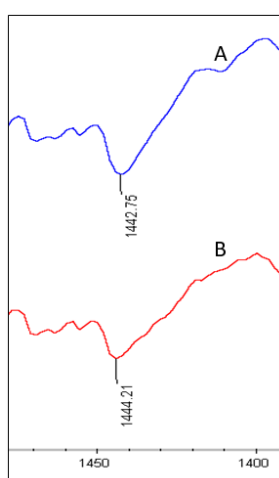
Figure 3.24 The FT-IR spectra of (A) pyridine + fresh $NiBr_2 \cdot 3H_2O$/[hmim][Br]; (B) pyridine + reuse $NiBr_2 \cdot 3H_2O$/[hmim][Br].

From FT-IR data, the system containing pyridine + fresh $NiBr_2 \cdot 3H_2O$/[hmim][Br] showed a single peak of C-H wagging of pyridine at 1442 cm^{-1} (Figure 3.24 (A)), while the C-H wagging peak of reused $NiBr_2 \cdot 3H_2O$/[hmim][Br] was shifted to 1444 cm^{-1} (Figure 3.24 (B)). Lewis acidity of reused $NiBr_2 \cdot 3H_2O$/[hmim][Br] increased more than that of fresh $NiBr_2 \cdot 3H_2O$/[hmim][Br]. The more Lewis acidity of reused $NiBr_2 \cdot 3H_2O$/[hmim][Br] would enhance the aldol condensation to produce 2,4-diphenylbutyl-2-enal (**4**). However, the increased acidity with reused $NiBr_2 \cdot 3H_2O$/[hmim][Br] was not effective for **α**-methylstyrene oxide (**6**). That was because **α**-methylstyrene oxide (**6**) had steric effect of methyl group at **α**-carbon.

In addition, 2-bromo-2-phenylethanol (**3**) could transform to 2,4-diphenylbutyl-2-enal (**4**) by being abstracted bromide form $NiBr_2 \cdot 3H_2O$/[hmim][Br]. That might cause the ionic liquid system to loss the activity, and then the system was unable to reuse for the next cycles.

3.5.3 Comparative study between $NiBr_2 \cdot 3H_2O$ and anhydrous $NiBr_2$ in [hmim][Br] on styrene oxide (1) rearrangement.

$NiBr_2 \cdot 3H_2O$ in [hmim][Br] could be applied to a variety of commercially available aryl epoxides providing good yield of desired products. However, $NiBr_2 \cdot 3H_2O$/[hmim][Br] could not reuse with the reaction of using styrene oxide. Some researchers reported that water could affect the product distribution. Aqueous medium could affect nucleophilic ring opening of 1,2-epoxide [45]. So, the examination of two nickel reagents $NiBr_2 \cdot 3H_2O$ and anhydrous $NiBr_2$ for styrene oxide (**1**) rearrangement was carried out and the results are reported in Table 3.6.

Table 3.6 Comparison between $NiBr_2 \cdot 3H_2O$ and anhydrous $NiBr_2$ in [hmim][Br] on styrene oxide (**1**) rearrangement.

Entry	Nickel complexes	% **1** (recovered)	Product (%)				Selectivity (2/(3+4+5))	Mass Balance
			2	**3**	**4**	**5**		
1	$NiBr_2 \cdot 3H_2O$	0	76	9	5	9	2.38	99
2	anh.$NiBr_2$	0	84	1	15	-	5.25	100

Reaction conditions: styrene oxide (**1**) (1 mmol), nickel reagent (1 mmol), [hmim][Br] (0.5 g) at 120 ^{o}C for 15 min.

Under the same conditions explored, anhydrous $NiBr_2$ provided higher selective ((**2/(3+4+5)**), 5.25) of phenylacetaldehyde (**2**) than $NiBr_2 \cdot 3H_2O$ ((**2/(3+4+5)**), 2.38) on

styrene oxide (**1**). Anhydrous NiBr$_2$ reduced 2-bromo-2-phenylethanol (**3**). This observation was similar to the work of Zhang and colleagues who reported that hydrated nickel (II) halides (NiX$_2$·nH$_2$O X = Cl, Br, I) were able to promote β-haloamines from nucleophile substitution [46].

Not only anhydrous NiBr$_2$ reduced 2-bromo-2-phenylethanol (**3**), but also it provided high phenylacetaldehyde (**2**) and 2,4-diphenylbutyl-2-enal (**4**) more than NiBr$_2$·3H$_2$O. That was because anhydrous NiBr$_2$ had high acidity more than NiBr$_2$·3H$_2$O which could be supported FT-IR as shown in Figure 3.25.
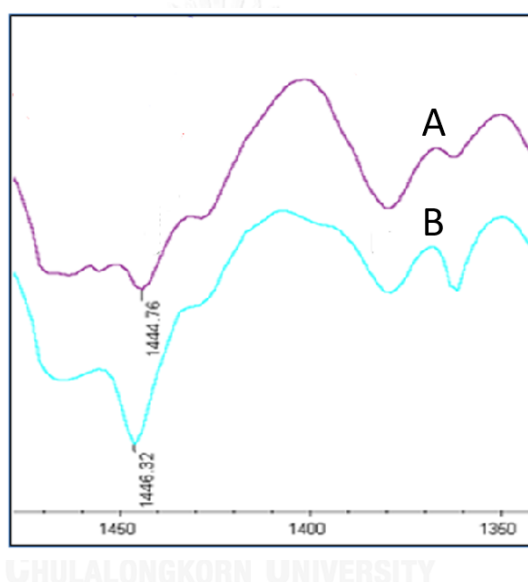
Figure 3.25 The FT-IR spectra of (A) pyridine + NiBr$_2$·3H$_2$O in [hmim][Br];
(B) pyridine + anhydrous NiBr$_2$ in [hmim][Br].

From the determination of Lewis acidities by FT-IR mentioned above, it was clearly indicated that Lewis acidity could be arranged in the order of anhydrous NiBr$_2$ + [hmim][Br] > NiBr$_2$·3H$_2$O + [hmim][Br]. The aldol condensation preferred more acidic condition. The higher Lewis acid of anhydrous NiBr$_2$ + [hmim][Br] could thus provide high yield of 2,4-diphenylbutyl-2-enal (**4**).

The activity of anhydrous NiBr$_2$ in recovered ionic liquid was tested in subsequent runs without addition of fresh reagent. The results are displayed in Figure 3.26.
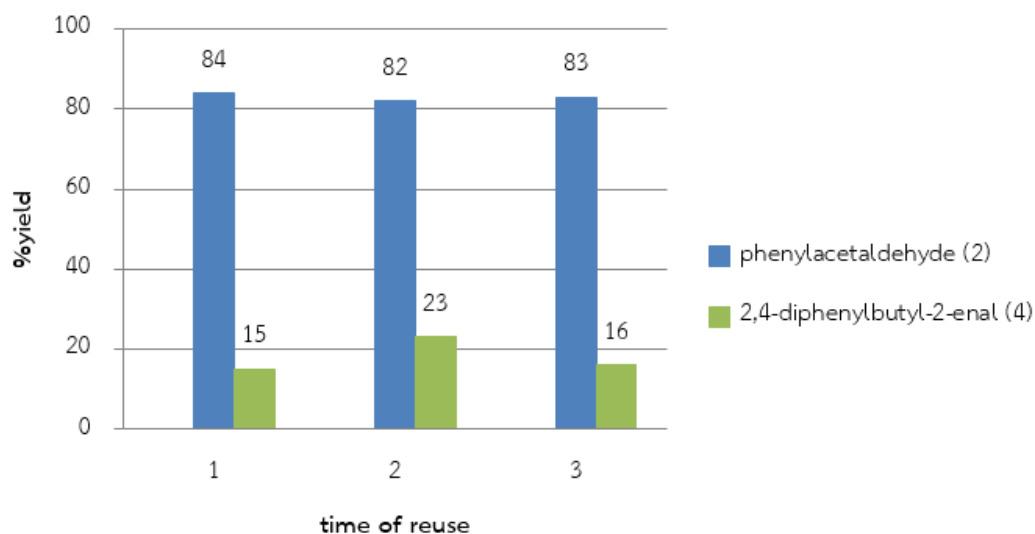
Figure 3.26 The reusability of the rearrangement of styrene oxide (**1**) mediated by anhydrous $NiBr_2$ in [hmim][Br].

The ionic liquid containing anhydrous $NiBr_2$ provided very good selectivity since anhydrous $NiBr_2$ did not provide 2-bromo-2-phenylethanol (**3**). The 82-84% yields of phenylacetaldehyde (**2**) were obtained. The anhydrous $NiBr_2$ in [hmim][Br] could be reused continuously three times without significant decrease in the activity of $NiBr_2$ in [hmim][Br]. So anhydrous $NiBr_2$ provided good reusability more than $NiBr_2 \cdot 3H_2O$.

3.6 The rearrangement of styrene oxide (1) with anhydrous $NiBr_2$ in [hmim][Br] assisted by microwave.

The research and application of microwave-assisted organic synthesis have led to the development of cleaner processes. The optimum conditions of the rearrangement of styrene oxide (**1**) by microwave-assisted was comparatively studied with normal protocol as presented in Figure 3.27.
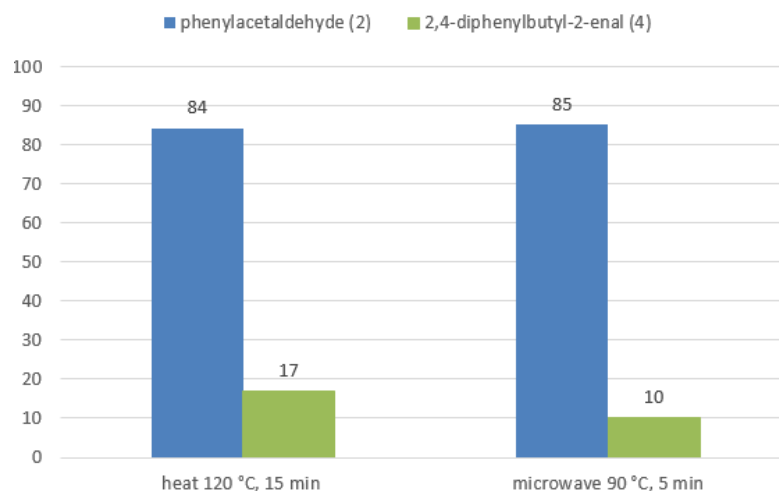
Figure 3.27 Comparative study between normal protocol (120 °C) and microwave on the rearrangement of styrene oxide (1) mediated by anhydrous $NiBr_2$ in [hmim][Br].

Microwave-assisted reaction was found to reduce the reaction time from 15 to 5 min. It helped the reduction of the reaction temperature from 120° to 90°C with similar yields. With their ionic character, ionic liquids absorb microwave irradiation extremely well and transfer energy quickly by ionic conduction. The reusability of ionic liquid by microwave was carried out and the results are presented in Figure 3.28.
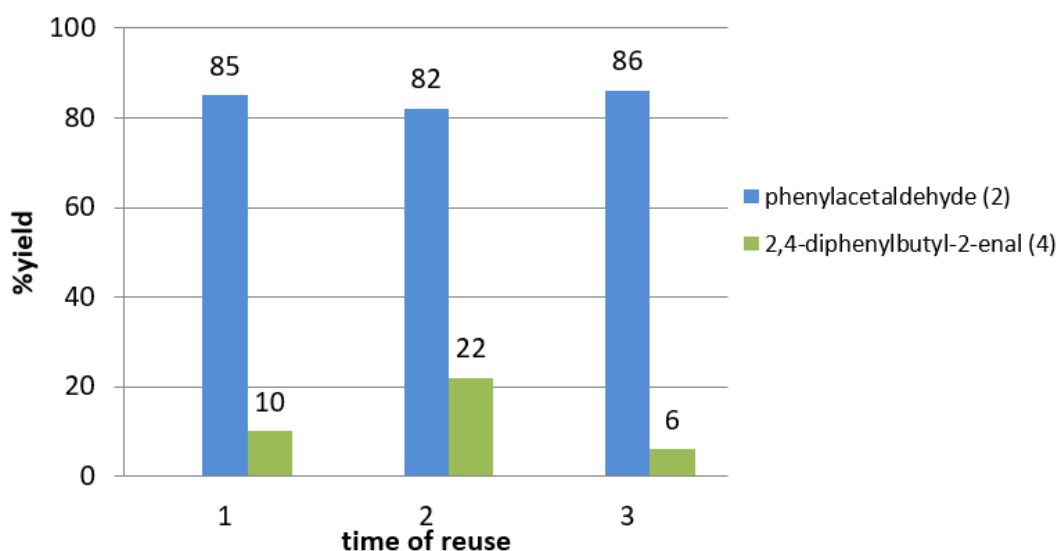
Figure 3.28 The reusability of the rearrangement of styrene oxide (**1**) mediated by anhydrous $NiBr_2$/[hmim][Br] used microwave at 90 °C for 5 min.

The activity of the recovered ionic liquid under microwave condition was tested in subsequent runs without addition of fresh anhydrous $NiBr_2$ for three runs. The yield of the phenylacetaldehyde (**2**) from the rearrangement of styrene oxide (**1**) was remained in 85, 82 and 86%, respectively. This yield has equally to normal heating method, but using shorter time and lower temperature than conventional methods. It was observed that this ionic liquid containing nickel salt displayed very good reusability, without significant loss of their activity (Figure 3.28). In addition this method was simple, highly efficient, necessitated short reaction time and low temperature.

CHAPTER IV

CONCLUSION

From the proceeding results and discussion, the optimum conditions were utilized to search for the simple and efficient method for the rearrangement of epoxides by nickel complex in ionic liquid. The study was carried out in the new system using $NiBr_2 \cdot 3H_2O$ in ionic liquid which was disclosed to be the most effective promoter on the epoxide rearrangement. The most appropriate conditions were the ratio 1:0.5 of $NiBr_2 \cdot 3H_2O$: [hmim][Br] at 120 $^{\circ}$C for 15 min. The 76% yield of the corresponding phenylacetaldehyde (**2**) was attained. Advantages of this method include the commercially available of nickel salt with low cost and rapid reaction.

This developed rearrangement system could be applied to other aryl epoxides. Applications on the rearrangements of aryl substituted epoxides were fruitfully achieved, the desired products were obtained in moderate to high yield with excellent selectivity.

The activity of the reused $NiBr_2 \cdot 3H_2O$ in [hmim][Br] was still viable in subsequent runs without addition of fresh nickel salt for five runs on α-methylstyrene oxide (**6**). However, the reuse of $NiBr_2 \cdot 3H_2O$/[hmim][Br] with styrene oxide (**1**) gave unsatisfactory result. Anhydrous $NiBr_2$ could be used to solve this problem because it provided high selectivity of phenylacetaldehyde (**2**).

The optimum conditions of anhydrous $NiBr_2$ were applicable to rearrange styrene oxide (**1**) under microwave. Microwave could reduce reaction time from 15 to 5 min and reduce the temperature of reaction from 120° to 90°C, without significant loss of their activity. This new system was found to be simple, highly efficient and short reaction time for the rearrangement of aryl epoxides.

Propose for the future work

This research concerned with the methodology development for the rearrangement of epoxides by nickel complex in ionic liquid. The outcome opened many possibilities to deal with future exploration. A commercially available $NiBr_2 \cdot 3H_2O$ in [hmim][Br] was utilized for the epoxide rearrangement. Although the low vapor pressure of ionic liquid may reduce the air pollution with respect to the typical volatile organic solvents, this is not enough for green process. So the propose for the future work should focus on the design of green processes. The development of ionic liquid containing ester groups in the alkyl side chain should improve biodegradability of ionic liquids. Biodegradable ionic liquids is the disintegration of materials by bacteria, fungi, or other biological means. This present examination is a profitable example for the methodology in crucial chemical reaction nowadays, and may be one of valuable chemical processes in the near future.

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APPENDIX

Table A.1 Crystal data of structure of $NiBr_2$ in [emim][Br]

Empirical Formula	$C_6H_{11}Br_4N_2\,Ni_2$
Formula Weight	409.58
Crystal Color, Habit	blue, prism
Crystal Dimensions	0.400 X 0.400 X 0.300 mm
Crystal System	Tetragonal
Lattice Type	I-centered
Lattice Parameters	a = 14.445(2) Å c = 19.527(3) Å V = 4074.5(10) Å^3
Space Group	I4$_1$/a (#88)
Z value	14
D$_{calc}$	2.337 g/cm^3
F$_{000}$	2716.00
μ (MoKα)	119.494 cm^{-1}

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Table A.2 Intensity measurements of X-ray diffraction.

Diffractometer	XtaLAB P200
Radiation	MoKα (λ = 0.71075 Å)
	graphite monochromated
Voltage, Current	50kV, 40mA
Temperature	-180.0 ˚C
Detector Aperture	83.8 x 70.0 mm
Data Images	721 exposures
ω oscillation Range (χ =25.0, ϕ =-108.0)	8.0 - 90.0˚
Exposure Rate	10.0 sec/˚
Detector Swing Angle	-0.14º
ω oscillation Range (χ=50.0, ϕ =-180.0)	-3.5 - 72.0˚
Exposure Rate	10.0 sec./˚
Detector Swing Angle	-0.14˚
oscillation Range (χ =25.0, ϕ =-36.0)	8.0 - 69.0˚
Exposure Rate	10.0 sec./˚
Detector Swing Angle	-0.14˚
ω oscillation Range (χ =12.0, ϕ =36.0)	29.0 - 89.0˚
Exposure Rate	10.0 sec./˚
Detector Swing Angle	-0.14˚
ω oscillation Range (χ =50.0, ϕ =108.0)	19.0 - 80.0˚
Exposure Rate	10.0 sec./˚
Detector Swing Angle	-0.14˚
ω oscillation Range (χ =50.0, ϕ =36.0)	12.0 - 33.0˚
Exposure Rate	10.0 sec./˚
Detector Swing Angle	-0.14˚
Detector Position	30.17 mm

Pixel Size	0.172 mm
$2\theta_{max}$	55.0°
No. of Reflections Measured	Total: 28345
	Unique: 2353 (R_{int} = 0.0486)
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.015 - 0.028)

Table A.3 Structure solution and refinement

Structure Solution	Direct Methods (SHELXS)
Refinement	Full-matrix least-squares on F
Function Minimized	Σ w $(F_o^2 - F_c^2)^2$
Least Squares Weights	w = 1/ [$\sigma^2(F_o^2)$ + $(0.0251 \cdot P)^2$ + 19.8660 · P] where P = $(Max(F_o^2,0) + 2F_c^2)/3$
$2\theta_{max}$ cutoff	55.0°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	2353
No. Variables	95
Reflection/Parameter Ratio	24.77
Residuals: R1 (I>2.00 σ (I))	0.0263
Residuals: R (All reflections)	0.0421
Residuals: wR2 (All reflections)	0.0656
Goodness of Fit Indicator	1.043
Max Shift/Error in Final Cycle	0.001
Maximum peak in Final Diff. Map	0.80 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.77 $e^-/Å^3$

VITA

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