ORGANIC CARBONATES AS BENIGN REAGENTS FOR THE SYNTHESIS OF FINE CHEMICALS USING SOLID ACID/ BASE CATALYSTS

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CERTIFICATE

This is to certify that the work incorporated in the thesis, **"Organic carbonates as benign reagents for the synthesis of fine chemicals using solid acid/ base catalysts"** submitted by **Mr. Anandkumar Balasaheb Shivarkar,** for the Degree of **Doctor of Philosophy,** was carried out by the candidate under my supervision in the Homogeneous Catalysis Division, National Chemical Laboratory, Pune – 411 008, India. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

March, 2007 **Dr. S. P. Gupte**

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DECLARATION

I hereby declare that the thesis **"Organic carbonates as benign reagents for the synthesis of fine chemicals using solid acid/base catalysts"** submitted for the degree of Doctor of Philosophy to the University of Pune has not been submitted by me for a degree to any other University.

March, 2007 **Anandkumar B. Shivarkar**

Pune

Dedicated to

My Parents

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ABSTRACT OF THE THESIS

The awareness for environmental protection has increased in the public, political and economical world over the past two decades, as quality of life is strongly connected to a clean environment.[1] Thus, though much progress has already been made the need for environmentally more friendly technology in the chemical industry is universally acknowledged. Fine chemicals are synthesis products aimed at chemical uses as an intermediates (or with the function of bulk chemicals), in the manufacture of various chemical substances such as: pharmaceuticals, flavors, agro-chemicals, personal-care chemicals and essences etc. Around 95% of all industrial heterogeneous catalysts are used in the production of bulk chemicals and only 3-5% in the synthesis of fine chemicals. In fine chemical industries, the low percentage use of heterogeneous catalyst accounts for approximately 20% of the profit. With respect to fine and intermediate chemicals manufacture, the profit margin seems to be much higher than in petrochemicals or refinery processes. That underlines the economic importance and the need of catalysis not only in the petrochemical industry but also in the specialty chemical production.[2]

In the manufacturing processes for fine chemicals, often stoichiometric amount of reagents, homogeneous acids and bases are still used to a great extent in the liquid phase which produces a lot of unavoidable side products and inorganic salts that are unacceptable from the environment aspects. In the development of cleaner technologies, catalysis in particular can contribute to a large extent.[3] Homogenous catalysis by soluble metal complexes[4] show high activity and selectivity at mild operating conditions and is finding wide application in both bulk and fine chemicals for a number of processes

involving carbonylation, hydroformylation, oligomerization, isomerization, polymerization and oxidation. The main drawback of homogenous catalysis is the separation of the catalyst and products. Subsequently, only 20% of the industrial catalytic reactions involve homogenous catalysis, while 80% employing heterogeneous catalysis.[2]

In particular, the challenges in fine chemicals synthesis are in the replacement of conventional catalysts and reagents based route which are corrosive, toxic, and produce inorganic salts that causes environmental problems. Some examples of undesirable reagents used for carboxylation and alkylation are phosgene, methyl halides and dimethyl sulfate (DMS).

The main objective of this present work was to develop more efficient and more selective catalyst systems and development of greener routes for the synthesis of fine chemicals using organic carbonates as benign reagents. Organic carbonates such as dialkyl carbonate (e.g. dimethyl carbonate)[5] and alkylene carbonate (e.g. ethylene carbonate, propylene carbonate)[6] are non-toxic, biodegradable and produced commercially via benign routes, replace potentially hazardous routes that uses phosgene and DMS to produce fine chemicals such as carbamates, *N*,*N*-dialkyl anilines and β-amino alcohols. These chemicals find wide range of applications in pharmaceuticals, agriculture industry and polymer industries. It is also the aim of this investigation to study chemical kinetic and mechanism of these reactions.

With these objectives, the following specific reactions have been studied.

- Carbamate synthesis via transfunctionalization of substituted ureas and carbonates
- Selective synthesis of *N*,*N*-dimethyl anilines from aromatic amines and dimethyl carbonate

- Synthesis of β-amino alcohols from aromatic amines and alkylene carbonates
- Tandem synthesis of β-amino alcohols from aromatic amines, dialkyl carbonates and ethylene glycol
- Kinetic and mechanistic study of β-amino alcohol synthesis from aniline and ethylene carbonate in presence of Na-Y zeolite as catalyst.

The thesis is presented in five chapters, a brief summery of which is outlined bellow.

CHAPTER 1. INTRODUCTION AND LITERATURE SURVEY

Chapter 1 presents a detailed literature survey along with objectives and scope of the present work on following reactions

- Carbamate synthesis
- *N*-alkylation reaction for synthesis of *N*,*N*-dialkyl anilines
- *N*-alkylation reaction for synthesis of β-amino alcohols

CHAPTER 2. CARBAMATE SYNTHESIS VIA TRANSFUNCTIONALIZATION OF SUBSTITUTED UREA AND ORGANIC CARBONATE

This chapter presents a detailed study on the synthesis of carbamates via transfunctionalization of substituted ureas and organic carbonates using homogeneous as well as heterogeneous catalysts which was demonstrated for the first time. This methodology is simple, environmentally benign and highly efficient for carbamate synthesis, and shows 100% atom economy. Excellent yield of carbamates were obtained by using homogeneous dibutyl tin oxide (DBTO) as a catalyst. Heterogeneous reusable silica gel catalyst was also found to be giving excellent yield of carbamates. Catalyst recycles study showed that there was no loss in catalytic activity of silica gel even after five recycles. The reactivity study of substituted ureas and organic carbonate was

investigated and it was observed that aliphatic ureas showed higher reactivity compared to aromatic ureas due to their basicity. Presence of various electron donating or electron withdrawing substituents (e.g. CH_3, Cl and NO_2) on aromatic urea did not show any significant effect on urea reactivity compared to non-substituted aromatic urea i.e. diphenyl urea. The reactivity of alkyl carbonates towards ureas was found to decrease in the order, dimethyl carbonate > diethyl carbonate > dibutyl carbonate as steric hindrance increased from dimethyl carbonate to dibutyl carbonate. The effects of reaction parameters on the synthesis of industrially important methyl *N*-methyl carbamate were also investigated. The Arrhenius activation energy for the reaction between *N,N'*-dimethyl urea and dimethyl carbonate was found to be 34.3 KJ/mol. A reaction mechanism has been postulated explaining the role of DBTO in the synthesis of carbamate from urea and carbonates. Synthesized carbamates were characterized by GC-MS, IR, NMR and elemental analysis.

CHAPTER 3. SYNTHESIS OF *N,N*-DIMETHYL ANILINES FROM AROMATIC AMINES AND DIMETHYL CARBONATE

In this chapter, selective *N,N*-dimethylation of aromatic amines with dimethyl carbonate in presence of water using simple and efficient catalysts consisting of onium salts and immobilized ionic liquid was demonstrated. It was observed that activity of immobilized ionic liquid, Cat-1 (TOF; 0.2 $^{-1}$h) is almost ten times less than homogeneous TEAB catalyst (TOF; 2.25 $^{-1}$h). Water played an important role in increasing the selectivity of *N,N*-dialkylated products (~99%) by hydrolyzing the side product such as carbamates to amines. Reactivity study of aromatic amines and organic carbonate was investigated and excellent yield of dialkyl products were obtained in case of anilines

having electron donating substituents on their ring and low yields for electron withdrawing substituents on anilines. The activity of dialkyl carbonates as alkylating agents towards aniline was found to decrease in the order, dimethyl carbonate > diethyl carbonate > dibutyl carbonate as steric hindrance increases from dimethyl carbonate to dibutyl carbonate. The effect of various process parameters on the synthesis of *N*,*N*-dimethyl aniline from aniline and DMC was also investigated. The catalyst recycle experiments showed that there was no loss in catalytic activity for both catalysts (TEAB and Cat-1) even after several recycles. Even though, both the catalysts show good recyclability, homogeneous TEAB catalyst suffers from energy intensive recovery procedures.

CHAPTER 4. SYNTHESIS OF β-AMINO ALCOHOLS FROM AROMATIC AMINES AND ALKYLENE CARBONATES

This chapter presents a detailed study on the synthesis of β-amino alcohols from aromatic amines and alkylene carbonates using solid acid/base catalysts. Excellent yields of β-amino alcohols as well as chiral amino alcohols were obtained from alkylene carbonates and chiral alkylene carbonates respectively by using highly efficient and reusable Na-Y zeolite as catalyst. It has been also shown that alkylene carbonates have excellent reactivity and at the same time they are non-toxic and safer to work with and can effectively replace the use of epoxides in the synthesis of β-amino alcohols. Reactivity of aromatic amines and alkylene carbonates was studied and it was observed that electron-donating substituents enhance the nucleophilicity of aniline thus increasing the reactivity as well as yield of β-amino alcohols, while electron-withdrawing substituents on the aniline ring decrease the reactivity as well as yield. It was found that

ethylene carbonate showed highest reactivity and the order of reactivity obtained was ethylene carbonate > 1,2 propylene carbonate > styrene carbonate > 1,3 propylene carbonate.

In this work, tandem synthesis of β-amino alcohols from aniline, dialkyl carbonate and ethylene glycol was also demonstrated for the first time. In this synthesis, ethylene carbonate was generated in-situ by transesterification reaction of dialkyl carbonate and ethylene glycol which reacted further with aniline to give β-amino alcohol. This reaction system was investigated in high-pressure as well as in pot reaction conditions. Various process parameters were investigated for the reaction of aniline, dimethyl carbonate and ethylene glycol under high-pressure reaction condition, it was observed that selectivity of mono β-amino alcohol i.e. *N*-phenyl ethanolamine was very poor (55%). The selectivity of *N*-phenyl ethanolamine was decreased due to the formation of *N*-methyl *N*-phenyl ethanolamine by *N*-methylation of *N*-phenyl ethanolamine in presence of dimethyl carbonate under high pressure condition. The selectivity of mono β-amino alcohol was improved drastically (91-99%) by carrying out the reaction under pot reaction conditions using diethyl carbonate or dibutyl carbonate. It was observed that Na-Y catalyst was highly effective in converting various anilines to β-amino alcohols in high yield with good catalyst recyclability. Reactivity of various aromatic anilines and dialkyl carbonates (as transesterification agent) was studied and it was observed that aromatic amines were showing same reactivity pattern which was observed in the reaction of anilines and alkylene carbonates. In case of screened dialkyl carbonates, diethyl carbonate was found the most suitable transesterification agent for tandem synthesis of β-amino alcohol as it was not a good *N*-alkylating agent, thus

selectively β-amino alcohols were formed. Dimethyl carbonate was highly reactive which gave more *N*-methylated products that decreased the selectivity of β-amino alcohol. Dibutyl carbonate was less reactive for transesterification reaction that resulted in poor yield of β-amino alcohol. Synthesized β-amino alcohols were characterized by IR, NMR and GC-MS analysis.

CHAPTER 5. KINETIC AND MECHANISTIC STUDY OF β-AMINO ALCOHOL SYNTHESIS FROM ANILINE AND ETHYLENE CARBONATE USING NA-Y ZEOLITE AS CATALYST

In this work, kinetics of *N*-alkylation of aniline by ethylene carbonate using a Na-Y zeolite as catalyst was studied in a batch reactor in the temperature range of 393-433 K. The reaction was found to be first order with respect to aniline concentration and first order tending to zero order with respect to ethylene carbonate concentration. A rate equation was derived using a catalytic cycle based on molecular level description of elementary steps and assuming adsorption of ethylene carbonate on Na-Y zeolite catalyst followed by reaction with aniline as the rate determining step. The kinetic parameters were estimated using non-linear regression analysis and activation energy was evaluated (83.1 KJ/mol).

This chapter also presents, detailed mechanistic studies of *N*-alkylation of aniline using ethylene carbonate in presence of Na-Y catalyst to β-amino alcohols by *in situ* FTIR spectroscopy (DRIFT technique).[7] In this study, various *insitu* adsorption experiments on Na-Y catalyst such as, pyridine adsorption, aniline adsorption, sequential adsorption of aniline and ethylene carbonate, ethylene carbonate adsorption, sequential adsorption of ethylene carbonate and aniline, adsorption of 1:1 mixture of aniline and ethylene carbonate on Na-Y catalyst and adsorption of aniline and ethylene carbonate on

4A catalyst were carried out. Based on these *in situ* experiments, reaction mechanism was proposed in which aniline activation on Lewis acid sites of Na-Y i.e. Na^+ was the first step; however ethylene carbonate did not get activated on the catalyst. The activated aniline acted as nucleophile and reacted instantaneously with ethylene carbonate liberating CO_2 to give product *N*-phenyl ethanolamine. This reaction was found to be occurring in the pores of the catalyst and not on the surface, which was confirmed by using 4A catalyst, which has only surface Lewis acidity and pore size which is smaller than size of aniline molecule.

The results of kinetic studies and *insitu* FTIR mechanistic studies for *N*-alkylation of aniline by ethylene carbonate indicate two different types of surface reactions that lead to amino alcohol formation. This may be due to the fact that the reaction conditions employed in kinetic studies and *insitu* FTIR mechanistic studies are completely different. In kinetic studies, liquid phase reaction occurs between aniline and ethylene carbonate in presence of triglyme as solvent using Na-Y catalyst, while in *insitu* FTIR mechanistic studies, pure aniline and ethylene carbonate react in vapor phase with Na-Y catalyst. Therefore, systems examined in kinetic studies and *insitu* FTIR mechanistic studies can not be compared and it is difficult to arrive at a common conclusion.

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Chapter 1

Introduction and Literature Survey

1.1. INTRODUCTION

The discovery and invention of new substances, which is the heart of chemistry, have proven to be the keystone to the improved well-being of mankind in the twentieth century. The discoveries of antibiotics, vaccines, and other modern medicines have contributed not only to the extension of the human life span by twenty-five to thirty years since the turn of the century, but also to the increase in the quality of human health. The development of effective fertilizers and pesticides has allowed crops to be grown and harvested in surplus quantities. Personal Quality of life has been improved enormously through the development of pharmaceutical, personal care products, polymer products and material science etc. At the center of these innovations, chemistry as well as catalysis has been both directly and indirectly involved in most of the technical achievements that characterize this century.[1]

Despite the enormous amount and type of technical advances in the twentieth century, the manufacture, processing, use and disposal of many of the chemical products on which society has grown to depend, have a negative impact on human health and environment. The toll on human as well as on the many ecosystems of the world is difficult if not impossible to assess in monetary terms. Although a monetary value can never be assigned to human life, recent studies have estimated the worth of the world's ecosystems to be as high as 33 trillion dollars, which is almost double the combined gross domestic product of the world's 194 nations.[2] Given such estimation, the cost of damage from chemical activity to the world's ecosystems clearly could be staggering.

A few notable environmental events that occurred in the past due to the undesirable impact of chemical activity, which affected human health and environment,

are the reasons for the concerns over the use of hazardous chemicals and their risk to human health and environment. Injudicious use of hazardous chemicals, pesticides (DDT) have an irreparable impact on avian species and thus damages the ecosystem.[3] Catastrophic events that took place in the past three decades such as, the chemical accident in Bhopal (India) and rampant water and air pollution (Cuyahoga river) became the subject of considerable public attention.

These environmental incidents over the past thirty years have shaped the public's opinion of chemicals and their effects on the environment and have also motivated the public as a whole to take steps through legislation and regulation. Socially, it is imperative that populace become aware of the innocuous and beneficial chemicals that have been manufactured and used, and that chemicals can be designed to be both safe and efficacious. Achieving these goals through the central science of chemistry is the primary objective of green chemistry.

1.2. GREEN CHEMISTRY

Definition[4]*- Green chemistry is "carry out chemical activities- including chemical design, manufacture, use and disposal-such that hazardous substance will not be used and generated."*

More broadly green chemistry is defined as the sustainable exercise of chemical science and technology within the framework of good practice of industrial ecology such that the use and handling of the hazardous substances are minimized and such substances are never released to the environment. A key aspect of green chemistry is sustainability; ideally, green chemistry is self-sustaining for several reason. Green chemistry is sustainable in term of material because of its minimum and efficient use of raw material.

Green chemistry is sustainable in term of waste because it does not create hazardous waste product. Green chemistry simply states that a central property or performance criterion of any chemical activity must be that it is benign to human health and the environment.

Of course, no chemical activity is ever completely innocuous or totally benign to human health and environment. Many companies have adopted goals of 'zero accidents' or 'zero defects', it is recognized that any goal of perfection is not fully attainable. It is also recognized that in setting goal, the value lies not in the actual goal but in the process of striving toward that goal. Striving toward nothing less than perfection ensures that improvement will always be sought in each step of the process.

1.2.1. GOAL OF GREEN CHEMISTRY[4]

The goal of green chemistry is to reduce the hazards associated with the product and processes and also maintain the quality of life. Risk can be summarized in simple term as the product of hazard of particular substance and the exposure to that substance.

$$\text{Risk} = \text{Hazard} \times \text{Exposure}$$

Green chemistry seeks to reduce the risk associated with the activity by reducing the hazard side of the risk if substance posses no significant hazard, there is no limit to the exposure to substance. Hazard is not simply defined as toxicity but it includes acute-chronic toxicity, carcinogenicity, flammability, direct ecological impact and atmospheric damage.

Along with this, there are general areas of investigation in green chemistry called as twelve principles of green chemistry, which can make ideal chemical synthesis.

1.2.2. TWELVE PRINCIPLES OF GREEN CHEMISTRY[5]

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. Use of auxiliary substances (e.g. solvents, separation agents etc.) should be made unnecessary wherever possible and, innocuous when used.
6. Energy requirements should be recognized for their environmental and economical impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical process) should be avoided whenever possible.
9. Catalytic regents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be developed further to allow for real-time in-process monitoring and control prior to the formation of hazardous substances.

12. Substances and form of substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires.

Tang et al.[6] have produced a simpler statement of the principles of green chemistry that is understandable to wide range of audience. Principles of green chemistry = productively.

P- Prevent wastes

r- Renewable materials

o- Omit derivatization steps

d- Degradable chemical products

u- Use safe synthetic methods

c- Catalytic reagents

t- Temperature, pressure ambient

i- In-process monitoring

v- Very few auxiliary substances

e- E-factor, maximize feed in product

l- Low toxicity of chemical products

y- Yes, it is safe

1.3. ROLE OF CATALYSIS FOR THE CLEAN PRODUCTION OF FINE CHEMICALS

Fine chemicals are synthesis products aimed at chemical uses as intermediates (or with the function of bulk chemicals), in the manufacture of various chemical substances such as: pharmaceuticals, flavors, agro-chemicals, hair dye, essences and detergents, etc.

Around 95% of all industrial heterogeneous catalysts are used in the production of bulk chemicals and only 3-5% in the synthesis of fine chemicals. In fine chemical industries, the low percentage use of heterogeneous catalyst accounts for approximately 20% of the profit. With respect to fine and intermediate chemicals manufacture, the profit seems to be much higher than in petrochemicals or refinery processes. That underlines the economic importance and the need of catalysis not only in the petrochemical industry but also in the specialty chemical production.[7]

Traditionally, fine and specialty chemicals have been produced predominantly using non-catalytic organic synthesis i.e. reagent based processes, which generate copious quantities of inorganic salts which is unacceptable from the environment aspects. Examples which readily come to minds are stoichiometric oxidations with permanganate, manganese oxide, chromium (IV) reagents, stoichiometric reductions with metal hydrides ($NaBH_4$, $LiAlH_4$, and variants thereof), reducing metals(Zn, Fe, Mg, Na) and a wide variety of reactions that employ stoichiometric quantities of Lewis acids ($AlCl_3$, BF_3, $ZnCl_2$) or mineral acids (H_2SO4, H_3PO_4, HF). All these processes produce a lot of waste which causes the extra burden on the ecosystem.

In the drive towards cleaner technologies, the entire arsenal of catalytic methodologies-homogeneous, heterogeneous and enzymatic catalysis-clubbed with organic synthesis will help to achieve the goal. All these approaches have their advantages and disadvantages. Homogenous catalysis by soluble metal complexes[8] is finding wide application in both bulk and fine chemicals for a number of processes involving carbonylation, hydroformylation, oligomerization, isomerization, polymerization and oxidation. These catalysts show high activity and selectivity at mild

operating conditions, ability to activate commercially available and cheaper substrates such as CO, hydrogen, olefins and alcohols and plausible characterization of reactions at a molecular level. There are several industrial processes based on homogenous catalysis such as, hydroformylation technology, Wacker process, carbonylation of methanol to acetic acid, ethylene polymerization by Zeigler-Natta catalysts and *p*-xylene oxidation to terephthalic acid etc. The main drawback of homogenous catalysis is the separation of the catalyst and products, which is often a tedious task involving precipitation of the catalyst by adding non-polar solvents, high vacuum distillation or extraction of products into a second phase, etc. subsequently, only 20% of the industrial catalytic reactions involve homogenous catalysis (Table 1.1),while 80% employ heterogeneous catalysis.

Heterogeneous catalysts are mainly divided in two categories: solid-acid and solid base catalyst.

1.3.1. SOLID-ACID CATALYSIS

Definition*[9]*: Solid-acid may be understood to be a solid on which the color of a basic indicator changes or a solid on which a base is chemically adsorbed or a solid acid shows a tendency to donate a proton or to accept an electron pair.

A wide variety of solid-acid catalysts are available: acidic clays, zeolites, silica-occluded hetropoly acids, sulfonated polysiloxanes, Nafion and variety of hybrid sulfonated mesoporous systems.

Table 1.1. Industrial processes using homogeneous catalysis

Sr. No	Process	Catalyst	Company
1	Oxidation of ethylene to acetaldehyde	$PdCl_2/CuCl_2$	Wacker-Werke [10]
2	Oxidation of p-xylene to terephthalic acid/ester	Co/Mn-salts	Imhausen
3	Polymerisation of ethylene to HDPE/LDPE	Ni-complex	Shell[11]
4	Hydrocyanation of butadiene to adipic acid	Ni-complex	Du Pont[12]
5	Asymmetric hydrogenation of acetamido cinnamicacid(3-methoxy -4-acetoxy derivative) (l-dopa process)	Rh(diene)(solvent)]+/DIPAMP	Monsanto[13]
		$NaCo(CO)_4$	BASF[14]
		$HCo(CO)_3PBu_3$	Shell[15]
6	Hydroformylation of propene to butyraldehyde	$HRh(CO)(PPh_3)_3$	UnionCarbide[16]Ruhrchemie -Rhone-Poulenc[17]
		Rh/TPPTS	
7	Hydroformylation of diacetoxybutene to 1-methyl-4-acetoxy butanal (Vitamin A intermediate)	$HRh(CO)(PPh_3)_3$	Hoffmann-La Roche[18]
		Rh catalyst	BASF[19]
		Rh/ Iodide	Monsanto[20]
8	Carbonylation of methanol to acetic acid	$Co_2(CO)_8$	BASF[21]
		Ir/Iodide	BPchemicals[22]
		Rh/MeI	Halcon[23]
9	Carbonylation of methyl acetate to acetic anhydride	Rh/MeI	Eastman Chemical[24]
10	Carbonylation of ethylene to propionic acid	$Ni(OCOC_2H_5)_2$	BASF[25]
11	Carbonylation of acetylene to acrylic acid	Ni-salts or carbonyls	BASF[26]
12	Carbonylation of benzyl chloride to phenyl acetic acid	$Co_2(CO)_8$	Montedison[27]
13	Carbonylation of 1-(4-isobutylphenyl)ethanol to Ibuprofen	$PdCl_2(PPh_3)_2/HCl$	Hoechst-Celanese[28]
14	Oxidative carbonylation of methanol to dimethyl carbonate	$PdCl_2$-$CuCl_2$	Assoreni [29]

These catalysts are used for various types of acid catalyzed reactions such as, electrophilic aromatic substitutions, e.g. nitration, halogenations, Friedel-Crafts alkylations and acylations, and numerous rearrangement reactions such as Beckmann and Fries rearrangements, and other reactions such as, cyclization and Diels-Alder reactions.

1.3.2. SOLID-BASE CATALYSIS

Definition[9]: Solid-base is defined as a solid on which the color of an acidic indicator changes or a solid on which an acid is chemically adsorbed or a solid base shows a tendency to accept a proton or to donate an electron pair.

The use of solid bases as catalysts in organic synthesis is less well-developed than solid-acid catalysis but is becoming increasingly popular.[30] For example, hydrotalcite anionic clays[31] alkali or alkaline earth metal occluded large pore zeolites and mesoporous silicas modified by surface attachment of organic bases[32] are effective catalysts for isomerization, Aldol, Knoevengel and related condensations that are widely used in fine chemical synthesis.

More than three hundreds of solid acids and bases have been developed in the last 40 years. Their surface properties and the structures have been identified by newly developed measurement methods using modern instruments and sophisticated techniques. The characterized solid acid/bases have been applied as catalysts for various reactions, and the role of their acid-base properties in catalytic activities and selectivities are being studied extensively. Now, solid acid-base catalysis is one of the economically and ecologically important fields in catalysis. They have many advantages over liquid Brønsted- and Lewis-acid and base catalyst. They are non-corrosive, easy to handle or transport and environmentally benign, presenting fewer disposal problems. Their repeated use and recovery from liquid products become much easier. Therefore, the replacement of the homogeneous catalyst with heterogeneous catalyst is becoming even more important in chemical and life science. Large numbers of industrial processes use solid acid/base catalysts such as zeolites (40% of all collected processes), complex

oxides, ion-exchange resins, phosphates, clays immobilized enzymes, sulfates plus carbonates and sulfonated polysiloxane (Table 1.2).

Table 1.2. Types of catalysts used in Industrial processes[30]

Sr.No.	Catalyst	No. of processes
1	Zeolites	74
2	Oxides, complex oxides	54
3	Ion-exchange resins	16
4	Solid acids (not specified)	7
5	Phosphates	16
6	Immobilized enzymes	3
7	Sulfate, carbonate	3
8	Clays	4
9	Sulfonated polysiloxanes	3

Based on above catalysts, industrial processes namely alkylation, isomerization, dehydration and condensation, amination, cracking and etherification, and the smaller ones for aromatization, hydration, hydrocracking, MTG/MTO, oligomerization, polymerization and esterification are carried out (Table 1.3A and 1.3B).

Table 1.3A. Industrial processes using solid acid-base catalysts[30]

Sr.No.	Type of reaction	No. of processes
1	Dehydration and condensation	18
2	Isomerization	15
3	Alkylation	13
4	Etherification	10
5	Amination	9
6	Cracking	8
7	Aromatization	7
8	Hydration	7
9	Oligomerization & polymerization	6
10	MTG/MTO-processes	5
11	Hydrocracking	4
12	Hydrogenation	4
13	Esterification	3
14	Disproportionation	2
16	MTBE-iC_4	1
17	Other	15
	Total	127

Table 1.3B. Industrial processes using Solid acid-base catalyst[30]

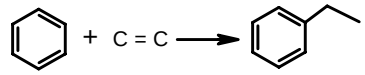
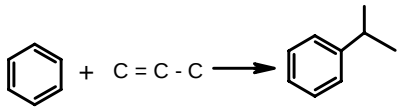
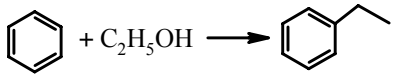
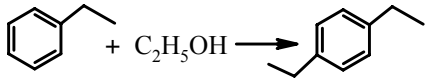
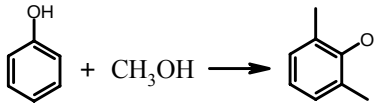
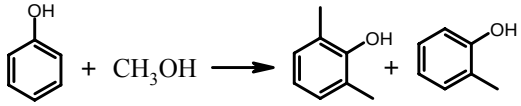
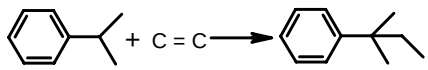
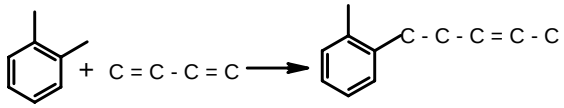
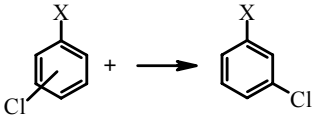
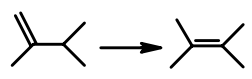
Sr.No	Process	Catalyst	Company
	Alkylation reaction		
1		H-ZSM-5	Mobil-Badger
2		High silica zeolite β-zeolite	Mobil-Badger /Raytheon Enichem
3		Pentasil zeolite Encilite 2	Hinduston Polymers
4		Pore size regulated ZSM-5	Paschim/IPCL
5		MgO	General Electric BASF AG
6		$Fe\text{-}V\text{-}O/SiO_2$	Asahi Chem.
7		$K/KOH/Al_2O_3$	Sumitomo Chemical
8		Na/K_2CO_3 basic catalyst	AMOCO Chemical, Teijin
	isomerization reaction		
9	Xylene isomerization ⟶ *p*-xylene	H-ZSM-5	Mobil Oil
10		High silica zeolite	Toray
11		H. ion-exchange resin	Exxon
12		Na/NaOH/g-Al2O3	Sumitomo Chemical
13	$n\text{-}C_4 \longrightarrow i\text{-}C_4$	Fe/Mn/sulfated ZrO2 Zeolite Zeolite	Sun Zeolite BP-Chemicals, Huntsman Shell

Table 1.3B. Continued

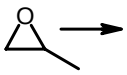
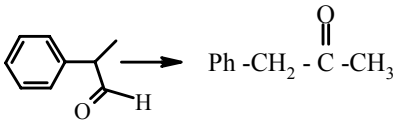
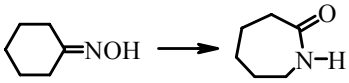
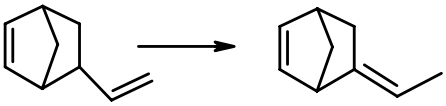
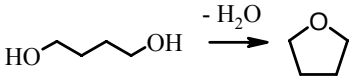
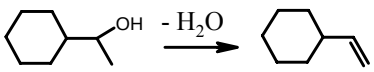
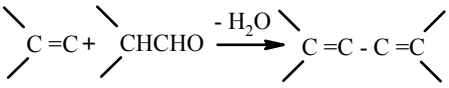
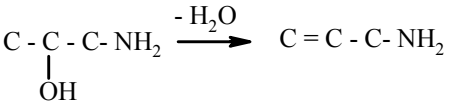
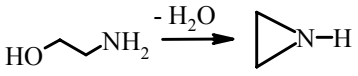
Sr.No	Process	Catalyst	Company
14	n-C'_4 ⟶ *i*-C'_4	SiO_2 modified Al_2O_3 Ferrierite B_2O_3/Al_2O_3	IFP Shell SNAM
15	$CH_2 = C = CH_2$ ⟶ $CH_3 - C \equiv CH$	K_2O/Al_2O_3	Shell
16		Li_3PO_4	ARCO
17		Pentasil zeolite	BASF AG
18		SAPO 11 High silicious Pentasil zeolite Ta-alkoxide/SiO_2	UCC Sumitomo Chemical Mitsubishi chem..
19		$Na/NaOH/Al_2O_3$	Sumitomo Chemical
	Dehydration and Condensation process		
20	EtOH $\xrightarrow{-H_2O}$ C_2H_4	Al_2O_3	Petrobrass
21	t-BuOH $\xrightarrow{-H_2O}$ *i*-C'_4	Sulfonic acid resin	UOP
22		Ion exchange resin	Davy-Mckee
23		ZrO_2-NaOH	Sumitomo
24		$Nb_2O_5.nH_2O$	Sumitomo
25		ZrO_2-KOH	Koei Chem.
26		Cs-Ba-P-O/SiO_2	Nippon Shokubai

Table 1.3B. Continued

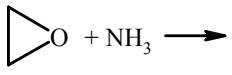
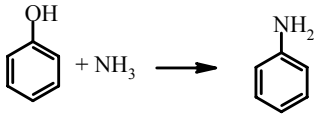
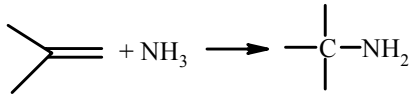
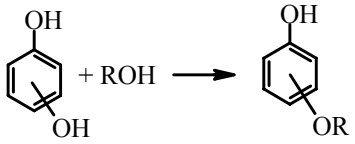
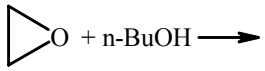
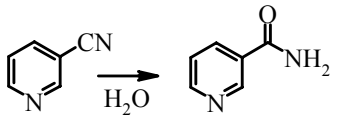
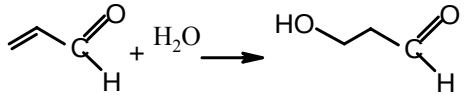
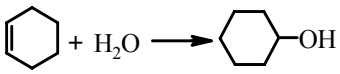
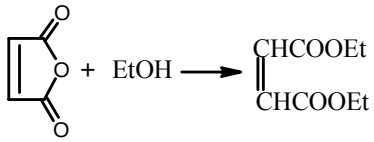
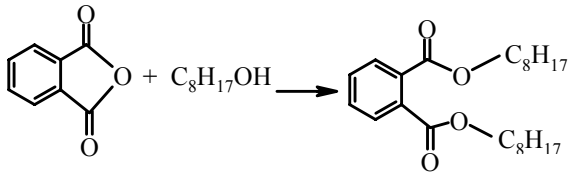
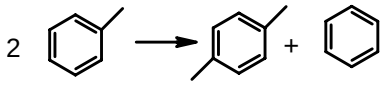
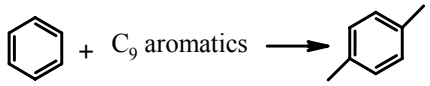
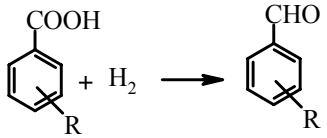
Sr.No	Process	Catalyst	Company
	Amination process		
27	$2MeOH + NH_3 \longrightarrow Me_2NH, MeNH_2$	RHO-ZK5 zeolite	Du pont
28	 $(OHCH_2CH_2)_2NH$; $OHCH_2CH_2NH_2$	Al-Si zeolite	Berol/Nobel
29		Mgo, B_2O_3, Al_2O_3 or TiO_2/SiO_2 or Al_2O_3	USS
30		Pentasil zeolite	BASF AG
	Cracking process		
31	FCC-processes	Novel Y/ SiO_2-Al_2O_3	Cosmo
32	Heavy oil	Mgo-Al_2O_3 -zeolite	Nippon oil
33	Deep cracking of vacuum gas oil	Pentasil zeolite	China petro
34	Selective cracking of straight chain paraffins and olefins to C_3' and c_4'	H-ZSM-5	Mobil
35	***Etherification processes***		
36	$i\text{-}C'_{4;} + MeOH \longrightarrow$ MTBE	Ion exchange resin	IFP, ACRO
37	$i\text{-}C'_{4;} + EtOH \longrightarrow$ ETBE	Ion exchange resin	SNAM
38	Olefinss + MeOH $\longrightarrow$ MTBE / TAME	Ion exchange resin	Erdoelchemi
39		Al-B-P-O	Ube
40	 ethyl ether of ethylene glycol	Pillared clay or smectite	BP
	Aromatization process		
41	C_3' C_4' to alkyl aromatics paraffins	ZSM-5	Mobil
42	LPG (mainly C_3, C_4) to BTX	Zeolite + promoter	UOP
43	LPG to aromatics	Metallosilicate	Mitsubishi oil
	Hydrocracking process		
44	Lub dewaxing; Wax+ H_2 tolower mol.wt. hydrocarbon	ZSM-5	Mobil
45	Hydrocracking of gas oils; Wax+ H_2 to gasoline	ZSM-5	BASF

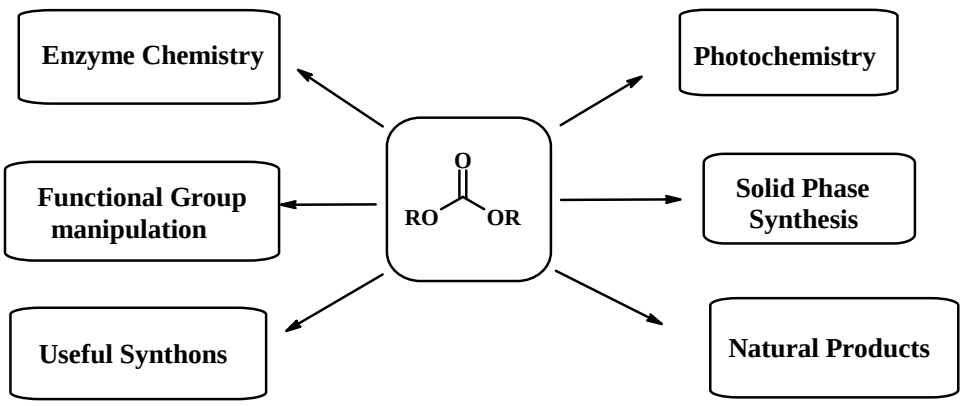
Table 1.3B. *Continued*

Sr.No	Process	Catalyst	Company
	Hydration process		
46	$C=C + H_2O \longrightarrow EtOH$	Solid phosphoric acid	Shell, BP
47		MgO	Distillers
		MnO_2	Reynolds Tobaco
48		Acid base catalyst on TiO_2/H_3PO_4	Degussa
49		Highly silicious H-ZSM-5	Ashi Chem.
	Esterification process		
50		Ion exchange resin	Davy-McKee
51		Mercapto functionalized sulfonated polysiloxane	Degussa AG
	Oligomerization & polymerization processes		
52	i-C_4 + butane to codimer	High SiO_2 mordenie	Tonen
53	C_3 to polypropylene	TiO_2 – MgO	China Petro
54	C_4 to linear octanes	H_3PO_4 / SiO_2	UOP
	Disproportionation process		
55		Zeolite ZSM-5	UOP Mobil
56		Zeolite	UOP
	Hydrogenation process		
57	$CO + H_2$ to gasoline	Zeolite	BP
58		ZrO_3-Cr_2O_3 Zeolite	Mitsubishi chem.. Crossfield

The main objective of this thesis was to develop greener routes for the synthesis of fine chemicals using organic carbonates as benign reagents. Fine chemicals such as, carbamates, dialkyl anilines and β-amino alcohols were synthesized, which have wide applications in pharmaceutical industries as drug intermediates, agriculture industries and useful as intermediates in the synthesis of perfumes, hair dyes and photo developers. This introduction chapter covers detailed literature survey on carbamate synthesis, dialkyl aniline synthesis and β-amino alcohols synthesis.

1.4. ORGANIC CARBONATE: AN ENVIRONMENTALLY BENIGN BUILDING BLOCK FOR ORGANIC REACTIONS

Organic carbonates stand on the verge of becoming extremely valuable tools to the organic chemist.[33] Organic carbonates are mainly used as carboxylating or alkylating agent in organic synthesis and have applications in medicine and polymer chemistry. A general overview regarding carbonate applications in organic synthesis is shown in Scheme 1.1.[33b]



Scheme 1.1. Applications of organic carbonates in organic synthesis

Use of organic carbonate in organic synthesis has become popular as DMC was produced in bulk quantity on commercial scale by benign routes.

1.4.1. VARIOUS ROUTES FOR SYNTHESIS OF DMC[34]

Conventionally DMC has been prepared by the reaction of methanol and phosgene in the presence of a concentrated NaOH solution. This route suffers from sever draw back of handling highly toxic and corrosive phosgene gas as well as environmental problem of disposing by-products.

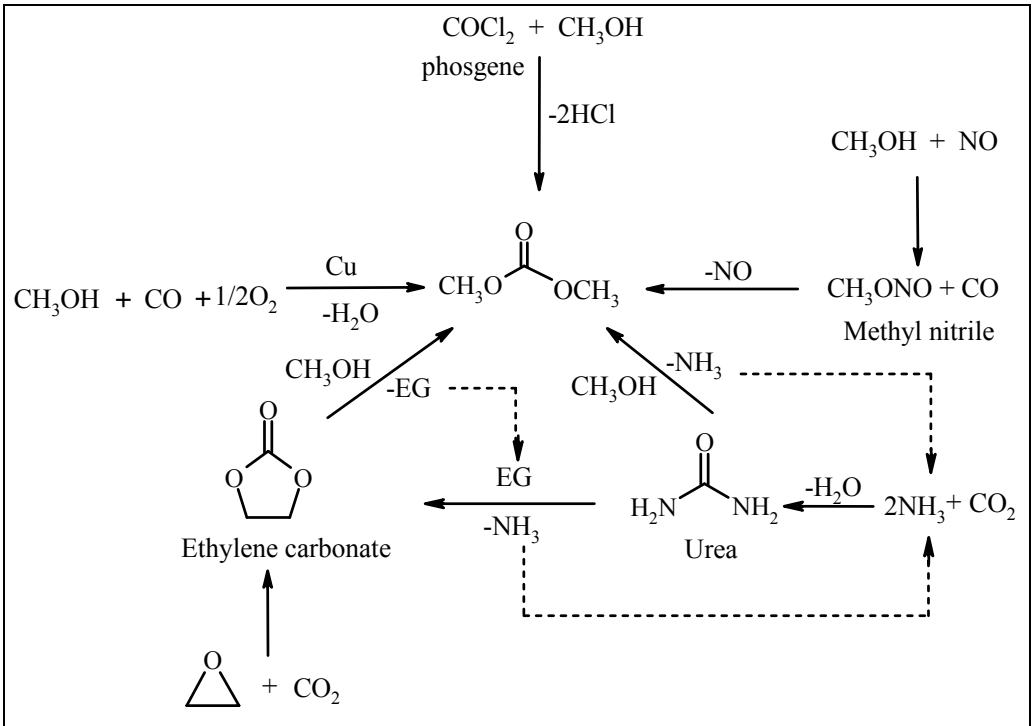
1.4.1.2. Non-phosgene processes for preparation of DMC

There are four non-phosgene routes for the production of DMC (Scheme 1.2)

1. Oxidative carbonylation of methanol is a non-phosgene route to DMC that is practiced commercially by EniChem, a major DMC producer (180 bbl/day). The process utilizes a copper chloride catalyst system. In the first step, copper is oxidized from the cuprous to the cupric state with the formation of cupric methoxy chloride intermediate. In the second step, the intermediate is reduced by carbon monoxide to give DMC and restore the cuprous chloride.
2. Ube has commercialized an oxidative carbonylation route that employs the use of nitric oxide as the redox agent. This route involves the formation of methyl nitrite from methanol, nitric oxide, and oxygen. Methyl nitrite is subsequently reacted with carbon monoxide to give DMC and releases nitric oxide for recycle. This approach eliminates the handling of solids/slurries as in the Enichem process.
3. DMC is also formed by the transesterification reaction between ethylene carbonate and methanol, giving ethylene glycol as a co-product. The DMC reactor

is assumed to be a boiling pot, operating at 423 K, surmounted by a trayed or packed section from the top of which DMC is distilled as the methanol/DMC azeotrope. Extractive distillation with water and a second column to remove water from DMC provides a pure product.

4. DMC is also formed by transfunctionalization reaction of methanol with urea using tin catalyst; however, yields are typically low because intermediate methyl carbamate is prone to decompose to isocyanic acid or isocyanuric acid. Catalytic Distillation Technologies has developed technology using high-boiling organic electron donor solvents, such as triethylene glycol dimethyl ether and tin-based catalysts, with continuous distillation of product dimethyl carbonate as it is formed



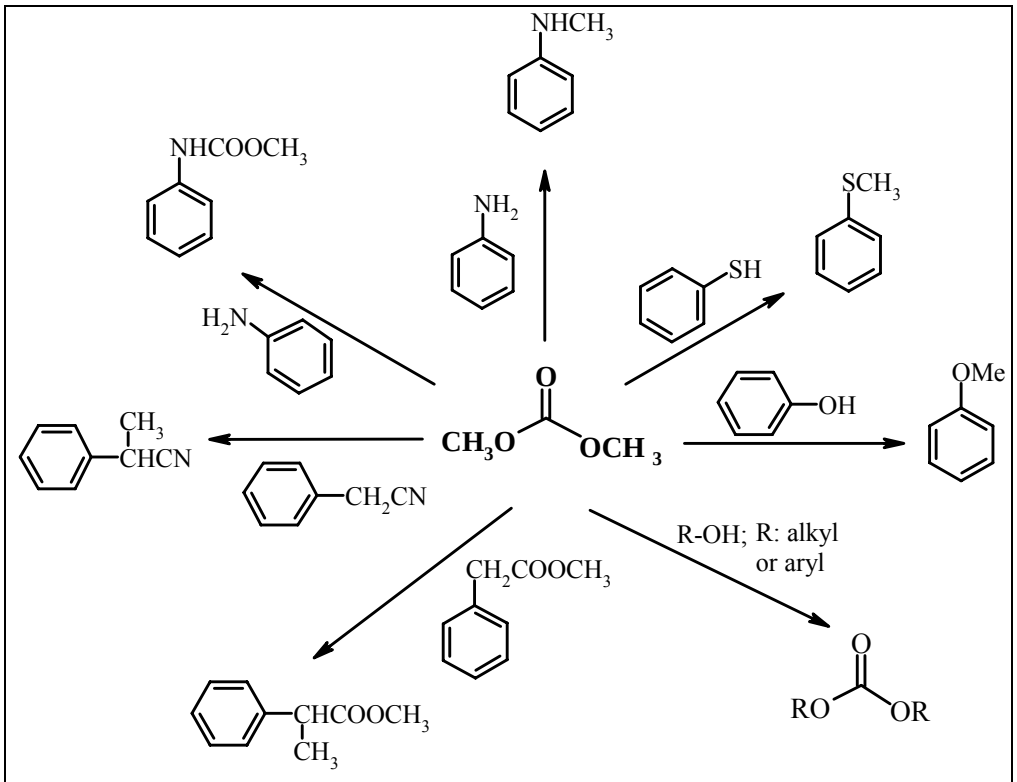
Scheme 1.2. routes to prparation of Dimethyl carbonate

In particular, an underdeveloped area of chemistry is in the replacement of reagents which are toxic, corrosive, dangerous, produced by eco-unfriendly processes and which produce inorganic salts those are expensive to dispose. Emblematic examples of undesired reagents used for methylation or carbonylation are methyl halide, dimethyl sulfate and phosgene. Organic carbonate such as dimethyl carbonate (DMC) possess two active reactive centers (alkyl and carbonyl carbon), whose reactivity can be tuned with the temperature and nature of nucleophile. This dual reactivity makes DMC a versatile intermediate for the replacement of dangerous chemicals such as phosgene for carbonylation and dimethyl sulfate (DMS) or methyl halide for alkylation reactions. Table 1.4 reports major environmental benefits of DMC-based procedures.[35]

Table 1.4. Comparison between DMC-and phosgene- or DMS- based reactions

Phosgene or DMS	**DMC**
Dangerous reagent (toxic, corrosive)	Harmless reagent (non-toxic, non-corrosive)
Use of solvent	No solvent
Waste water treatment	No waste water
Base consumption (e.g.NaOH)	The base is catalytic
By-products: NaCl, Na_2SO_4	By-product: MeOH, CO_2
Exothermic	Slightly or not exothermic

In many aspects, DMC used as an environmentally benign building block for organic reactions such as, carbamate synthesis, alkylation reaction such as, *C*- alkylation, *N*-alkyaltion, *O*-alkylation and *S*-alkylation and transesterification reaction for the synthesis of higher molecular alkyl carbonate and aromatic carbonates (Scheme 1.3).[33]



Scheme 1.3. DMC for environmentally benign organic reactions

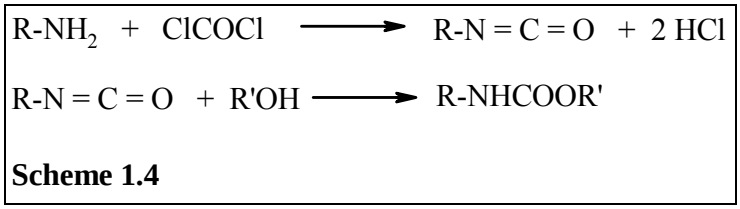
1.5. CARBAMATE

Carbamates are compounds of great interest because they exhibite some of the characteristic properties of carboxylic esters and amides and have a wide range of applications in chemical industry such as in the production of commodity chemicals like polyurethane, herbicides and pesticides.[36] On the other hand carbamates are required in the low volumes but high cost segment for the production of drug intermediates in pharmaceutical industry.[37] Carbamates play a key role in organic synthesis as protecting group[38] and in understanding of DNA structures.[39] 'Rubisco', a world's most abundant enzyme is a carbamate and plays an important part in fixation of CO_2 by photosynthesis.[40] Recently due to the development of combinatorial techniques in the

field of drug discovery and due to their medicinal and biological properties, carbamates have gained considerable importance in the preparation of small molecule libraries.[41]

1.5.1. SYNTHESIS OF CARBAMATE

The commercial production of carbamate is almost exclusively based on conventional phosgene technology (Scheme 1.4).[42] This process suffers from handling highly toxic and corrosive phosgene gas which produces HCl as a side product.



Scheme 1.4

In spite of the hazards involved in phosgenation process, the chemical industry still uses about 2×10^6 ton/year of phosgene worldwide[43], as economy still favors the phosgenation process. Although most of the use of phosgene is meant for captive consumption it causes tremendous burden on ecosystem in terms of waste disposal (use of 1 kg phosgene gives 1.17 kg of salt waste[44]) and air pollution. The preference for using phosgene by industry is mainly driven by the fact that phosgene technology is cheaper, simple and convenient hence seemingly overrides the danger of handling phosgene and isocyanates, [45] which is unavoidable in phosgenation of amines.

Carbamates were also synthesized by using various types of reagent and rearrangements (Scheme 1.5).[46]

1. $R\text{-}N = C = O + R'OH \longrightarrow R\text{-}NHCOOR'$

2. $R\text{-}NH_2 + ClCOOR' \longrightarrow R\text{-}NHCOOR'$

3. $ClCN + RCl + FeCl_3 \longrightarrow (RN = CCl_2)n\ (FeCl_3)_m$

   $(RN = CCl_2)n\ (FeCl_3)_m + R'OH \longrightarrow R\text{-}NHCOOR'$

4. $RCONH_2 + NaOBr \xrightarrow[\text{rearrangement}]{\text{Hoffman}} R\text{-}N = C = O \xrightarrow{R'OH} R\text{-}NHCOOR'$

5. $RCON_3 \xrightarrow[\text{rearrangement}]{\text{Curtious}} R\text{-}N = C = O \xrightarrow{R'OH} R\text{-}NHCOOR'$
   Pyrolysis

6. $RCONHOCOR \xrightarrow[\text{rearrangement}]{\text{Lossen}} R\text{-}N = C = O \xrightarrow{R'OH} R\text{-}NHCOOR'$
   Base

7. $RCOOH + HN_3 \xrightarrow[\text{rearrangement}]{\text{Schmidt}} R\text{-}N = C = O \xrightarrow{R'OH} R\text{-}NHCOOR'$
   H_2SO_4

8. $RNHCOCl_3 \xrightarrow{Na_2CO_3} R\text{-}N = C = O \xrightarrow{R'OH} R\text{-}NHCOOR'$

Scheme 1.5. Various routes for carbamate preparation

The routes mentioned above for carbamate synthesis either deals with handling of potentially hazardous chemicals or requires acid and bases in stoichiometric amount which produces inorganic salts that ends up with aqueous effluent.

Several efforts have been made for the preparation of carbamates using non-toxic reagents and for the development of novel environmentally friendly methodologies.

1.5.2. SYNTHESIS OF CARBAMATES VIA GREEN CHEMISTRY

Major routes for carbamate synthesis using green chemistry are shown below:

1. Carbonylation of nitro aromatics to carbamates
2. Oxidative carbonylation of amines to carbamates
3. Carboxylation of amines using CO_2
4. Carboxylation of amine using organic carbonates
5. Alcoholysis of urea

1.5.2.1. Carbonylation of nitro aromatics to carbamates

Industrially**,** aromatic isocyanates represent very important intermediates. Especially in polymer industries, poly isocyanates such as 2,4-toluene diisocyanate (TDI) or methylene 4,4'-diphenyl diisocyanate (MDI) are the starting materials for the synthesis of many polyurethanes.[47a] For aromatic isocyanate producers, the advantages of carbonylation processes staring from nitro aromatics were foreseen quite a some time ago and have attracted attention for more than 30 years.[47b]

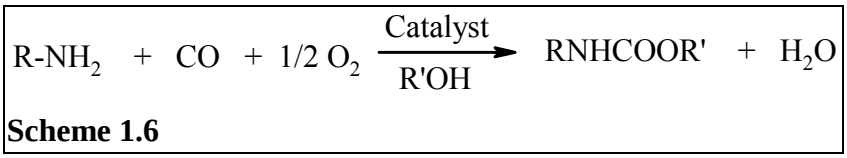
The use of carbon monoxide (CO) for reduction of nitrogen-oxygen aromatic bonds was initially reported in 1949 by Buckeley and Ray who converted nitrobenzene in azo benzene.[48] This discovery initiated the research on various reduction processes of the nitroso aromatic linkage assisted by transition metal complexes using CO.[49] Subsequently, in 1967, Hardy and Bennet reported the catalytic generation of isocyanates from nitro compounds using rhodium, palladium or other metal salts in the presence of a Lewis acid promoter.[50] Catalytic systems comprising various transition metal salts were then systematically studied. The catalyst system typically consists of a catalyst precursor used in conjunction with various promoters such as ligands or co-catalyst (mostly Lewis

acid) or both. Thus, the selectivity and conversion of the carbonylation reaction is dependant on the nature and properties of the precursors-ligands-promoters as well as on the temperature and CO pressure applied during the reaction. Typical reaction temperatures range between 393–493 K, whereas pressure usually lies between 4 to 20 MPa. For the synthesis of carbamates, various catalysts such as metals deposited on various solid supports in the presence of ligands[51] or system as (MX_n / ligand / Lewis acid) with $RhCl_3$ or $PdCl_2$ were active. New catalytic system with Ir or Pt complexes were also effective and performed like $PtCl_2(PPh_3)_2/SnCl_4$ precursors.[52]

Polynuclear precursors like carbonyl clusters of rhodium or ruthenium constituted much more active catalyst for carbonylation, especially when used with a co-catalyst like NEt_4Cl[53]. The presence of a co-catalyst was essential for the catalysis to proceed efficiently and specifically, for instance diamine ligand was required with Pd catalyst. Attempts to replace the diamine by diphosphine ligand or vice-versa in these systems often resulted in lower selectivity and yield.[54] Other new systems like ([Rh]/dppe)[55], ([Rh]/phen)[56] or ([Pd]phen/H^+)[57] have been thoroughly studied relative to the others. Very impressive results were obtained when Bronsted acid co-catalyst was replaced by Ce(IV) salt.[58] Other recently discovered active catalysts are ruthenium complexes of Schiff bases[59] or Pd salts with Keggin-type heteropolyanions ($PdCl_2$/HPA).[60]

1.5.2.2. Oxidative carbonylation of amines to carbamates in alcohol medium

Another notable environmentally benign synthesis pathway to carbamate is the oxidative carbonylation of amines with alcohol (Scheme 1.6).



Scheme 1.6

Oxidative carbonylation of aromatic amines to carbamate is reported to be effectively carried out using a variety of noble metal catalyst viz. Pd, Pt, Rh, Ir, Ru etc. in presence of promoters such as iodide ion and α.-benzoinoxim etc. under severe conditions of high pressure of $CO:O_2$ gas mixture and high temperature.[61] The selectivity and conversion of the carbonylation reaction is dependant on the type of catalyst used, concentration of amine, $CO: O_2$ ratio and temperature. Typical reaction temperatures range between 353 to 493 K, whereas pressure usually lies between 3 to 10 MPa. Se, Te and Co catalysts have also been used for carbonylation of aliphatic and alicyclic amines, but these catalysts show very low activity towards the carbonylation of aromatic compounds.[62] Alper and Hartstock[63] described a homogeneous $PdCl_2$-$CuCl_2$ catalyst for the carbonylation reaction at room temperature and atmospheric pressure. Wan et al.[64] have shown that the polymer-supported bimetallic catalyst (PVP-$PdCl_2$-$MnCl_2$) exhibits high activity and selectivity for the oxidative carbonylation of amines under atmospheric pressure in presence of base. Shi and Deng have reported a gold complex [($Au(PPh_3)$ Cl] as an active catalyst for oxidative carbonylation reaction for the first time.[65] These researchers have also developed a relatively simple catalyst system consisting of $PdCl_2$ and sulfated zirconia for the efficient synthesis of carbamates.[66] Recently F. Shi et al.[67] have developed an efficient catalyst system, Pd complex-ionic liquid, for the carbonylation of amines and shown the reusability of catalyst with slight loss in catalytic activity.

1.5.2.3. Carbon dioxide mediated carboxylation of amine to carbamate

The utilization of carbon dioxide in the synthesis of carbamates can represent an attractive alternate route to conventional phosgene or isocyanate based routes. This new procedure utilizes less noxious starting material such as CO_2, which responds to requirement of both environmental protection and utilization of CO_2 as a source of carbon (Equation 1.1).

$$RNH_2 + CO_2 + R'\text{-}X \longrightarrow RNHCOOR' + H\text{-}X \qquad (1.1)$$

Chisholm and Extine in 1977 showed that transition metal complexes of *N,N* dimethyl amide $M(Me_2N)_n$ add onto CO_2 giving metal carbamato derivatives.[68] Later Tsuda et al.[69] reported the catalytic conversion of amines and carbon dioxide to carbamates. Kojima et al.[70] found that aluminum porphyrine is able to activate CO_2 and the catalytic system thus generated yields carbamate from amine and epoxide under ambient condition with TON of ~ 35. Ruthenium catalyzed carboxylation of secondary amines and terminal alkynes has been reported to give enol carbamates in good yields with high regio and sterio selectivity.[71] Higher yields of carbamates were realized when alkyl halides and a suitable "host-guest" type of additives such as macrocyclic poly-ethers[72] or onium salts[73] or strong organic bases with the ability to delocalize their charge were employed as additives.

However, the disadvantage of this methodology was that it requires stoichiometric amount of alkyl halide and produces equal amount of halide salts as a waste.

1.5.2.4. Carboxylation of amine to carbamate using organic carbonate

Aminolysis of organic carbonates (Equation 1.2) has become a very attractive synthetic route to carbamate, since non-phosgene routes to carbonic acid diesters are now available.

$$RR'NH + R''OCOOR'' \longrightarrow RR'NHCOOR'' + R''OH \qquad (1.2)$$

R, R' = H, alkyl or aryl; R'' = alkyl or aryl

In fact, dimethyl carbonate (DMC) is currently produced on large scale by oxidative carbonylation of methanol (Enichem- Ravenna, Italy). Organic carbonates of high boiling alcohols[74] or phenols[75] can be obtained easily by trans-esterification of DMC or diethyl carbonate.

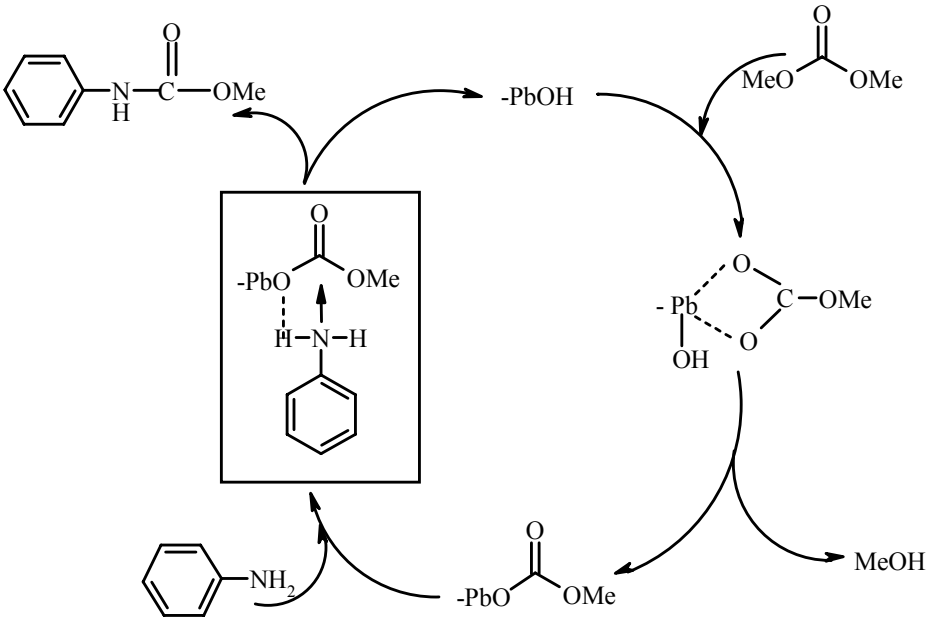
The reagent chemistry of organic carbonate has been developed by Ono[33a] and Tundo[33c,d] for synthesis of several important organic intermediates, establishing DMC as a benign building block for organic synthesis. Alkyl carbonates e.g. DMC show two sites for interacting with nucleophilic reagents: a) a methyl sp^3 carbon atoms; b) the carbonylic sp^2 carbon. So, DMC and more generally, dialkyl carbonates are interesting examples of ambident electrophilic substrates and the regioselectivity of the attack by nucleophiles is an important feature of the chemistry of these compounds. Reaction of amine and organic carbonate (Equation 1.2) usually needs a suitable catalyst to observe a good conversion rate and selectivity. Literature on carboxylation of amine to carbamate using organic carbonate is summarized in Table 1.5. Strong bases[76] such as alkali metal alkoxides, or Pb, Zn, Co, Sn, Al, Mn and Ti organometallic complexes andcompounds[77] have been widely used as catalyst in the carboxylation of anilines. More ever, Lewis acids, such as $AlCl_3$, $SnCl_2$, $ZnCl_2$, $Zn(OAc)_2$, $FeCl_3$ or metal (Rh, Ru) complexes have proved to be

effective catalysts.[78] Synthesis of carbamate from dialkyl carbonate and amines in the presence of γ-Al_2O_3,[79] MCM-41-TBD,[80] and $Yb(OTf)_3$[81] has been also reported. Sima and co-workers[82] have demonstrated alkoxy carbonylation of primary and secondary amines by DMC using ionic liquids (e.g. salts of substituted imidazolium). The ionic liquids function both as catalyst as well as solvents. In addition use of ionic liquid provides an efficient separation of products from catalyst components. Tundo et al. have also reported, CO_2 promoted Carboxylation of aliphatic amines to carbamate in excellent yield under super critical conditions (90 bar CO_2; 130 ºC).[83] Extensive screening study on micro porous and mesoporous zeolites and metal oxides catalysts has been reported for synthesis of methyl *N*-phenyl carbamate from DMC and aniline.[84]

1.5.2.4.1. Mechanisms for Carboxylation of amines by organic carbonates to carbamate

1.5.2.4.1.1. Pb Catalysts

Fu and Ono[78b,c] have reported the mechanism for amine carboxylation reaction using Pb compounds. They proposed that Pb species serves as a Lewis acid to enhance the polarization of the carbonyl group of DMC. The surface PbOH groups interact with DMC to form PbOCOOMe groups, which in turn react with aniline to form carbamate and regenerate the surface PbOH groups (Scheme 1.7).

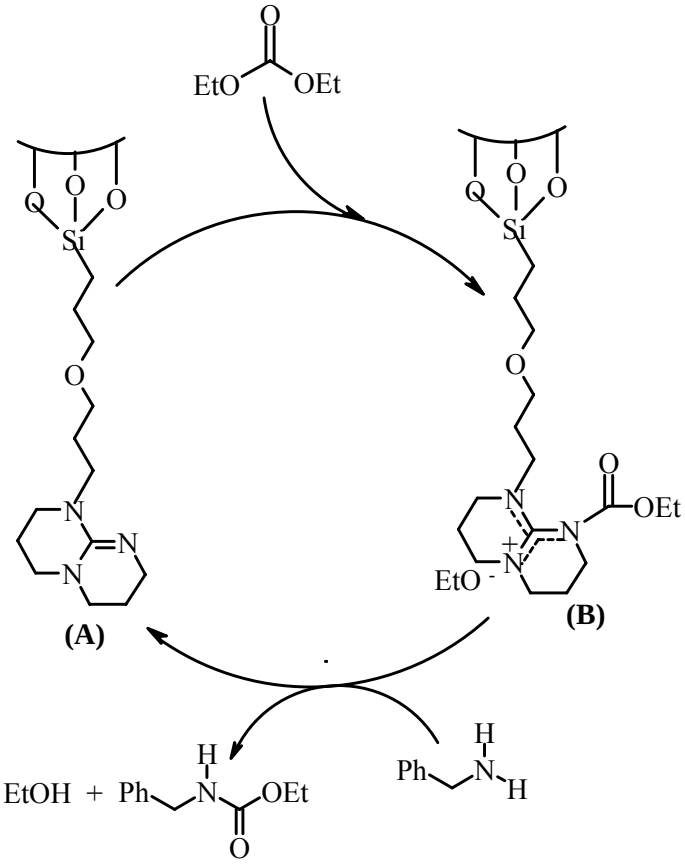


Scheme 1.7. Proposed mechanism of carboxylation of amine using Pb catalyst

1.5.2.4.1.2. MCM-41-TBD catalysts

Carloni et al.[80] have reported the mechanism for amine carboxylation reactions using MCM-41-TBD catalyst (**A**). They proposed that all the transformations may have resulted from a catalytic cycle, depicted in Scheme 1.8. As strong base, supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) is sufficiently nucleophilic to attack on the carbonyl group of diethyl carbonate, giving the guanidinium salt **(B).** Subsequent attack of the amine on the activated carbonyl group of **(B)** gives the carbamate and restores the catalyst. This step is particularly favored since the positive charge, delocalized over the three nitrogens, promotes the nucleophilic attack on the carbonyl, enhancing its electrophilic character. Though the counter ion EtO^- is an actually abase catalyst, the authors proved that ethoxide is not the catalyst by carrying out the reaction with ethoxide.

No reaction was observed which confirmed that the real catalyst is TBD and not the ethioxide.



Scheme 1.8. Hypothesized reaction mechanism for carboxylation of amine using MCM-41-TBD catalyst

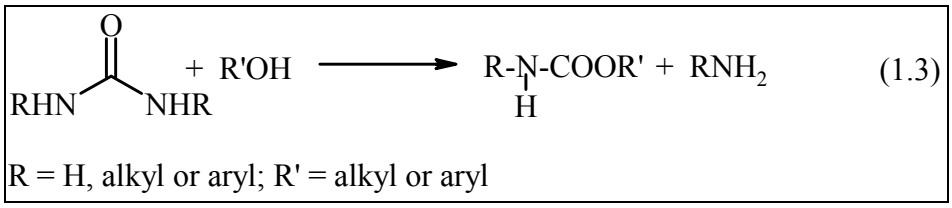
Table1.5. Literature on carboxylation of amine using organic carbonate

Sr. No.	Substrate	Organic carbonate	Catalyst	Time; h	Temp. ^{0}C	Amine Conv. %	Carbamate Yield, %	Reference
1	C_6H_5-NH_2	DMC	PbO (red)	1	160	98	97	Fu & Ono[78b]
2	C_6H_5-NH_2	DMC	$Zn(OAc)_2.H_2O$	1	160	93.3	91.3	Fu & Ono[78b]
3	n-C_4H_9-NH_2	DEC	NaH	1	25	-	70	Angeles et al.[76d]
4	*m*-Cl-C_6H_4-NH_2	DEC	NaH	1.5	25	-	93	Angeles et al [76d]
5	C_6H_{13}-NH_2	DMC	$Pb(NO_3)_2$	2	120	99	99	Baba et al.[78d]
6	C_3H_7-NH_2	DMC	$Pb(NO_3)_2$	2	100	98	93	Baba et al.[78d]
7	C_6H_5-NH_2	DMC	γ-Al_2O_3	48	90	100	95	Vauthey et al.[79]
8	*p*-Cl-C_6H_4-NH_2	DMC	γ-Al_2O_3	48	90	100	85	Vauthey et al.[79]
9	$C_{10}H_{21}$-NH_2	DMC	$scCO_2$	17	130	96	83	Tundo et al.[83]
10	$C_{10}H_{21}$-NH_2	DEC	$scCO_2$	20	130	80	65	Tundo et al.[83]
11	n-C_4H_9-NH_2	DMC	$Yb(OTf)_3$	8	80	-	93	Curini et al.[81]
12	C_6H_5-NH_2	DMC	$Yb(OTf)_3$	8	80	-	96	Curini et al. [81]
13	*p*-NO_2-C_6H_4-NH_2	DMC	$Yb(OTf)_3$	8	80	-	61	Curini et al. [81]
14	C_6H_5-CH_2-NH_2	DEC	MCM-41-TBD	24	125	99	98	Carloni et al.[80]
15	C_6H_{11}-NH_2	DEC	MCM-41-TBD	24	125	92	90	Carloni et al.[80]
16	C_6H_{11}-NH_2	DMC	BMImCl	1	170	100	83	Sima et al.[82]
17	C_6H_5-CH_2-$N(CH_3)H$	DMC	BMImCl	1	170	100	99	Sima et al.[82]

DMC: dimethyl carbonate; DEC: diethyl carbonate

1.5.2.5. Alcoholysis of urea

Alcoholysis of urea is another important phosgene free route for carbamate synthesis (Equation 1.3).



Alcoholysis of urea is the preferred commercial route to methyl or ethyl carbamate synthesis.[85] Hofmann studied the preparation of ethyl carbamate by heating urea and ethanol under pressure at 423 K.[85c] Higher temperatures is necessary for the optimum dissociation of urea to the reactive intermediates - cynic acid and ammonia. Only that alcohol with a boiling point above 413–423 K gave good yields of carbamates. In 1946, Paquin reported the catalytic effect of various metal salts on the rate of reaction of an alcohol with urea. By using heavy metal salts of weak organic acids, or zinc and cobalt chlorides, alkyl carbamates were obtained in high yields (>90%) with shorter heating cycles.

There is only scanty information available on alcoholysis of substituted urea and the patented literature in this field mainly discloses the process and yield of carbamate.[86] Ball et al.[87] have studied the reaction between aromatic or aliphatic alcohols and urea. The reaction of urea with aliphatic alcohols leads to carbamate formation selectively using tin complexes as catalyst while, aromatic alcohols lead to side product formation such as isocynic acid, which decreases yield of carbamate.

1.6. *N*- ALKYLATION

Alkylations are among the most important reactions in organic chemistry. *N*-alkylated derivatives of aromatic amines such as *N*-alkyl (e.g. *N*-methyl aniline) and *N,N*-dialkyl (e.g. *N,N*-dimethyl aniline) derivatives are useful intermediates in the manufacture of dyes, pharmaceuticals, agrochemicals, plastic and explosives.[88]

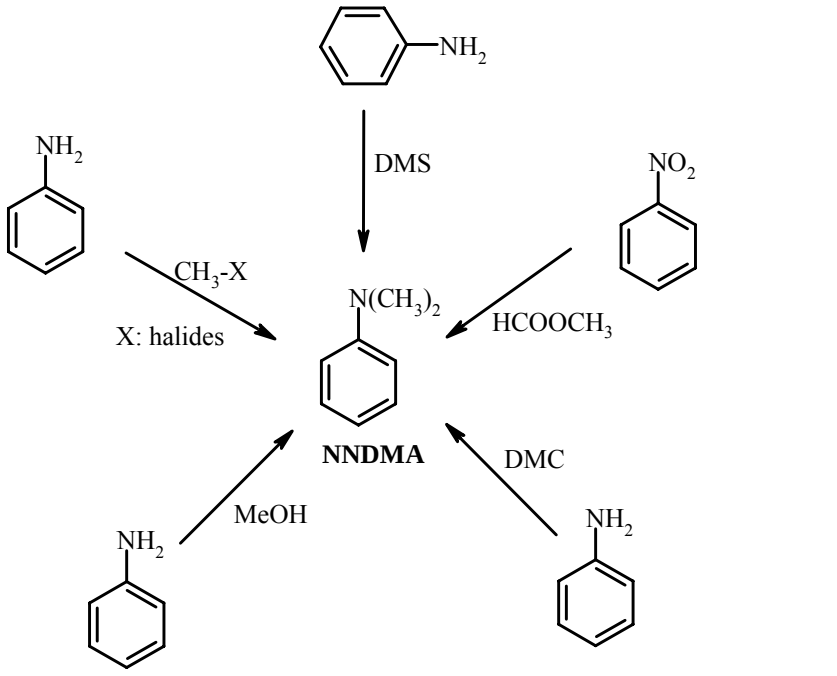
The most common methods of alkylation use dimethyl sulfate[89] and alkyl halides[90] as the alkylating agents. There are, however, significant disadvantages in carrying out alkylations with these reagents:

1. Dimethyl sulfate (DMS) and methyl halides are toxic and also corrosive. Therefore, acid-resistant materials must be used for the construction of reactors.
2. Since the reactions proceed in the basic media, stoichiometric amounts of bases are required to neutralize the acid that is formed. This results in the stoichiometric formation of inorganic salts, which have to be disposed properly.

The first disadvantage may be overcome by using non-toxic alkylating agents such as methanol and dimethyl carbonate (DMC), though these reagents are not so reactive. To avoid second disadvantage mentioned above, the stoichiometric reactions must be replaced by catalytic reactions.

1.6.1. SYNTHESIS OF *N,N* -DIMETHYL ANILINES

N,N-dimethyl anilines are valuable intermediates in the synthesis of pharmaceuticals, agrochemicals and dyes as well as fine chemicals such as Vanillin, Michler's ketone etc. Various routes[91] for the synthesis of *N,N*-dimethyl anilines have been shown in Scheme 1.9.



Scheme 1.9. routes for synthesis of *N,N*- dimethyl aniline synthesis

1.6.1.1. Methanol as an alkylating agent

Conventionally, NNDMA was synthesized from the reaction of aniline and methanol under pressure by using mineral acids[92] (H_2SO_4) catalysts. (Scheme 1.10)

$$C_6H_5NH_2 + CH_3OH \longrightarrow C_6H_5NHCH_3 + H_2O$$

$$C_6H_5NHCH_3 + CH_3OH \longrightarrow C_6H_5N(CH_3)_2 + H_2O$$

Scheme 1.10

This is a two-step process and a study of its kinetics shows that reaction rate is proportional to the concentration of aniline in the first step and the concentration of *N*-methyl aniline (NMA) in the second step. With 50% excess methanol, the reaction equilibrium reaches to 99% *N,N*-dimethyl aniline (NNDMA) at 493 K. But at higher

temperature, ring alkylation and formation of formaldehyde from oxidation of methanol, are observed. This traditional route of liquid phase alkylation using mineral acids and $AlCl_3$ as catalyst suffer from the disadvantages of high capital cost, reactor corrosion, formation of by-products and the difficulties in handling and regeneration of catalysts.

With the increasing awareness of environmental issues, various solid acid catalysts have been tested for their activity in alkylation reactions in place of traditional Friedel-Crafts catalyst and mineral acids, the subject has been reviewed by Narayanamn and Deshpande.[93] Vapor-phase *N*-alkylation of aniline was initially studied by Hill et al using Al_2O_3 as a catalyst.[94] Later on, the gas-phase reaction involving aniline alkylation with methanol was extensively studied using several different kinds of materials such as, clays, zeolites, metal oxides, metal sulfates and aluminophosphates. Layered double hydroxides (LDH) known as hydrotalcites (HT)[95a] and Zn-Co-Fe ternary spinel system[95b] have also been studied for this reaction, wherein NMA formed selectively. In case of ZSM-5 catalyst, the extent of conversion using this material increases with increasing aluminum content.[96] The vapor phase *N*-alkylation of amine reaction has also been catalyzed by AlPO4-5, AlPO4-11, CoAPO-5, CoAPO-11, ZAPO-5 and ZAPO-11 with the formation of NMA, NNDMA and *N*-methyl toluidine (NMT) where the product distribution has been found to be influenced by the space velocity and the aniline to methanol ratio.[97] *N*-methylation products have been found to be as being predominant over Al-HMS mesoporous molecular sieves,[98] γ-alumina[99] and metallosilicates.[100] A vapor-phase continuous process for the production of NNDMA from aniline and methanol has been described using alumina based solid catalyst, wherein ~86% yield of NNDMA has been claimed.[101] Zeolites X and Y ion-exchanged with Li, Na, K, Rb and

Cs also have been used for this reaction. NNDMA is produced mainly over zeolite X and NMA produced over zeolite Y.[102] A mixture of N and C-alkylated products can be obtained over the more acidic form of the zeolite. A rapid deactivation of zeolite-X has been also reported. A review on the aniline alkylation over the solid acid catalyst also appeared and the results suggests that the major factors influencing the activity and selectivity of the gas phase alkylation of aniline are the acid-base properties and shape selectivity of the solid catalyst.[93] Grace et al.[103] studied the alkylation of aniline with methanol over cocrystalized zeolite RHO- zeolite X (FAU) and over zeolite Linde type L (Sr, K-LTL) as catalysts. They observed that NNDMA was formed with (> 90%) selectivity using cocrystalized zeolite RHO- zeolite X (FAU).

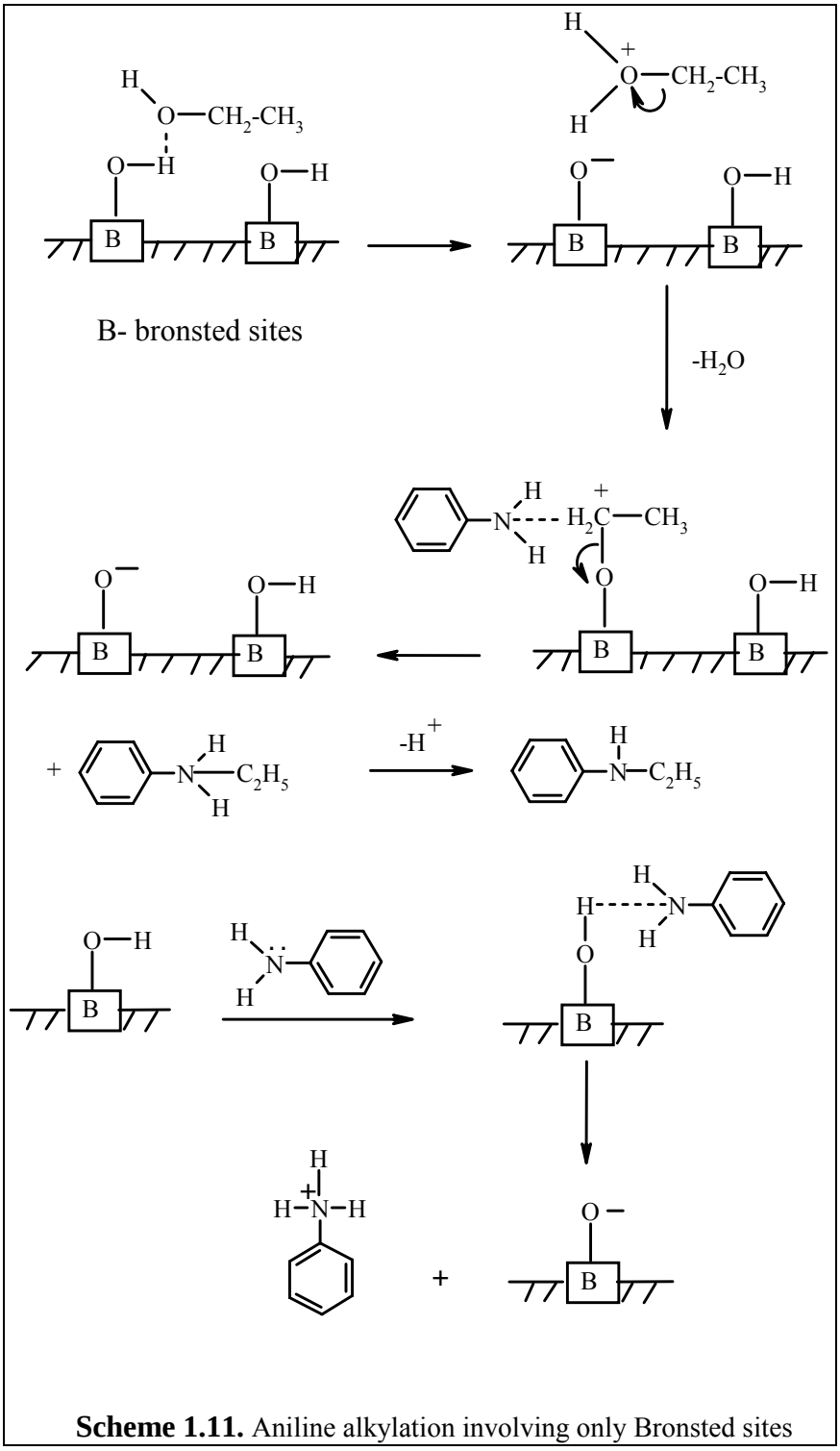
1.6.1.1.1. Mechanism of alkylation

Narayanan and Deshpande[93] have proposed a mechanism for the *N*-alkylation reaction under different conditions of the catalyst containing:

1. Only Brønsted acid sites
2. Only Lewis acid sites
3. Both Brønsted and Lewis acid sites.

1.6.1.1.1.1. Catalyst having only Brønsted acid sites

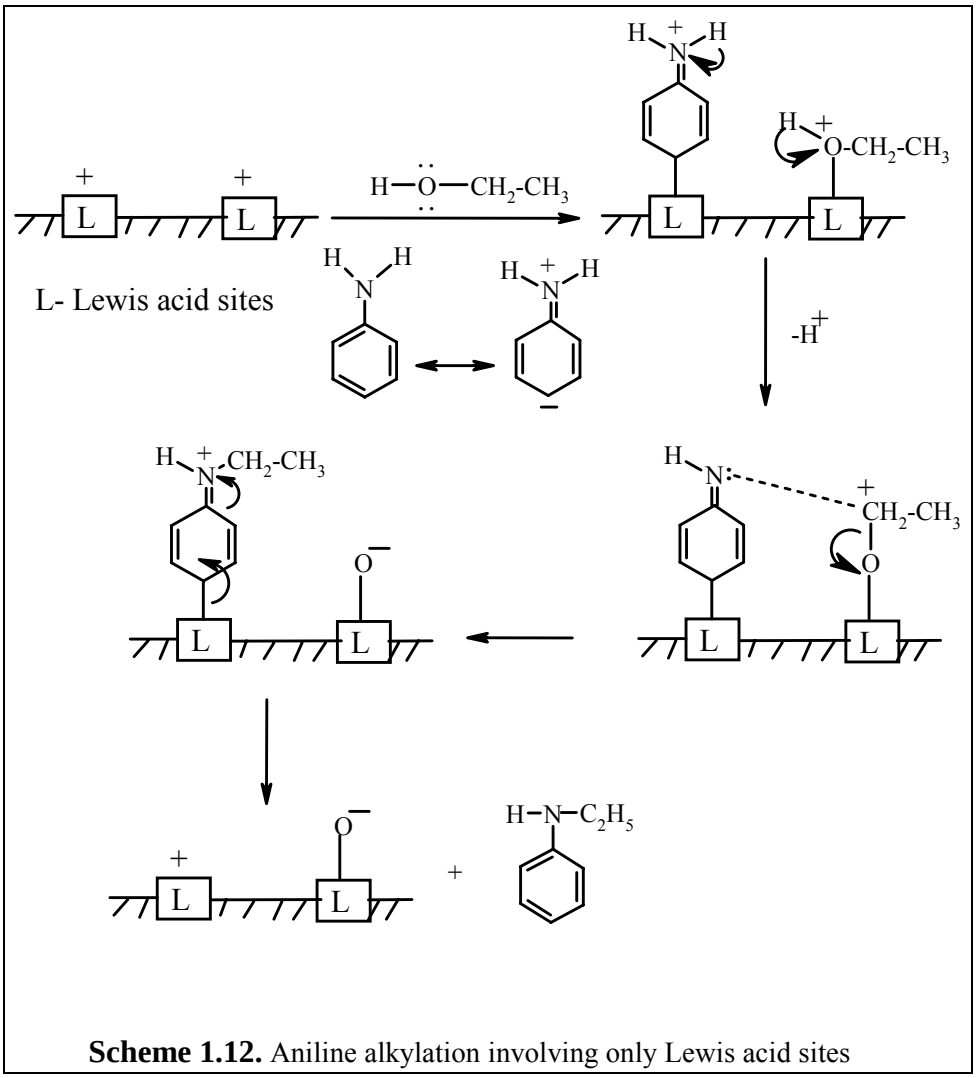
Aniline alkylation on catalyst having only Brønsted acid sites is a situation very similar to that present on silica catalyst. Weak Brønsted acidity of silica is responsible for dehydration reaction of alcohol to give carbocation. On the other hand, aniline gets protonated to give anilinium ion bringing down the rate of reaction (Scheme 1.11). This may be reason for the comparatively low aniline alkylation activity of silica.



Scheme 1.11. Aniline alkylation involving only Bronsted sites

1.6.1.1.1.2. Catalyst having only Lewis acid sites

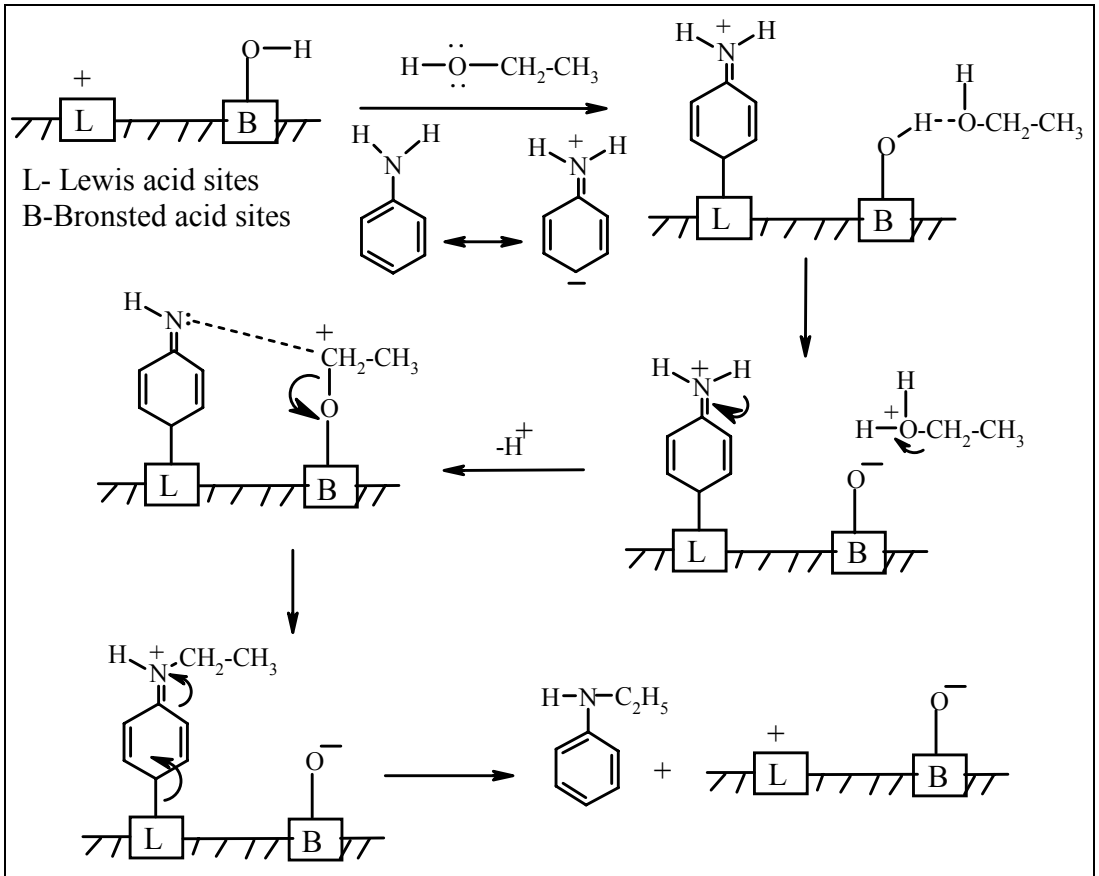
Aniline being a stronger base than ethanol gets absorbed preferentially on the Lewis acid site. However, the presence of a large excess of alkylating agent, does not rule out the possibility of ethanol getting absorbed on the acid sites as well. Having a catalyst system with exclusively Lewis acid sites is rather unlikely under the reaction conditions involving dehydration of alcohol. Even if the catalyst does not posses the Brønsted hydroxyls to start with, it may eventually develop them during the course of alkylation in presence of H_2O released in the course of reaction (Scheme 1.12)



Scheme 1.12. Aniline alkylation involving only Lewis acid sites

1.6.1.1.1.3. Catalyst having both Brønsted and Lewis acid sites

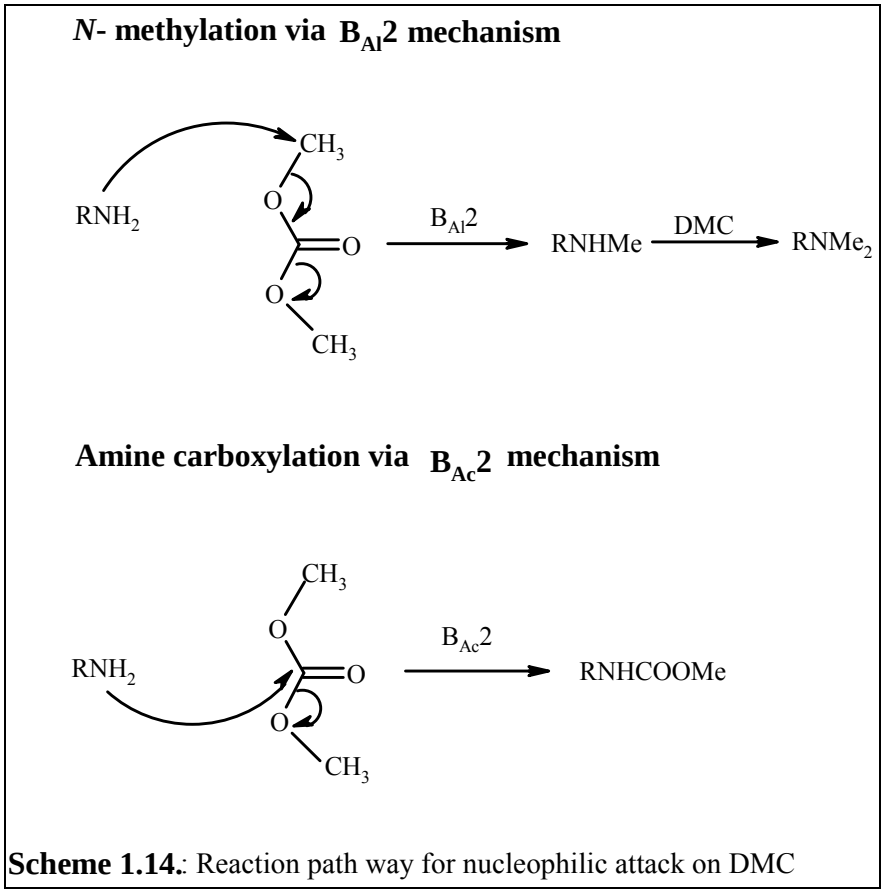
Basic aniline preferentially gets absorbed on Lewis acid sites, while ethanol is bound to the hydroxyl protons of Brønsted acidic sites through the oxygen by hydrogen bond. Protonation of alcohol, dehydration and subsequent formation of ether of the released carbocation with conjugate base of Brønsted acid site may follow. On the Lewis acid site, the absorbed aniline loses a proton to balance the positive charge developed on the nitrogen. The high electronegativity of oxygen in the ether linkage results in the development of a partial positive charge on the alkyl side chain, initiating heterocyclic cleavage of polar O-C bond and the shift of alkyl carbocation to nitrogen (Scheme 1.13).



Scheme 1.13. Aniline alkylation involving both bronsted and Lewis acid sites

1.6.1.2. Dimethyl carbonate as an alkylating agent

Dimethyl carbonate has a versatile chemical property and has been used mainly as a methylating and methoxycarbonylating agent. These reactions are very important in organic synthesis. The use of DMC as a methylating agent has become popular as it is produced commercially by environmentally benign routes. Tundo et al.[104] have shown that the attack of nucleophile on DMC (having two reactive centers; methyl sp^3 carbon atom and carbonylic sp^2 carbon) is taking place by two different paths as shown in Scheme 1.14.



Scheme 1.14.: Reaction path way for nucleophilic attack on DMC

The vapor phase *N*-alkylation of aniline using DMC as well as DEC as an alkylating agent was extensively studied.[105] It was shown that with faujasite as catalysts, DMC as methylating agent was quite selective for *N*-alkylation of aniline. Ono et al.[105a] have reported high yield of NMA with 92% selectivity using Na-X catalyst at 423 K, while at 513 K temperature NNDMA was produced with > 95% selectivity. Zeolite K-EMT and K-Y were also selective catalysts for formation of NMA (99.6% conversion with 93.5% NMA selectivity), while alkaline X zeolites were the best catalysts for the production of NNDMA (75% selectivity at 97% conversion).[106] Barthomeuf et al. studied this reaction over different zeolites having both acid and basic sites. They observed that the C- alkylation with DMC may be favored on protonic sites, while *N*-methylation may occur on other active centers such as basic or Lewis acid sites present in the alkaline samples.[106]

Liquid-phase *N*-methylation of anilines have been studied by Tundo and coworkers using faujasites X and Y catalysts.[107] They reported that mono methyl anilines were formed selectively (>95%) with only traces of dimethyl derivatives at 403–453 K temperature. Romano et al.[108] have reported excellent yield of NNDMA (85%) with 15% yield of NMA at 421 K temperature using methyl iodide as catalyst. Shen and Jiang showed that diphenylammonium triflate (DPAT) was an excellent catalyst for selective synthesis of *N*,*N*-dimethyl anilines (> 99.6%).[109] Recently Selva et al.[110] showed selective *N*,*N*-dimethylation of primary aromatic amines (90 to 96%) using unsymmetrical methyl alkyl carbonate in presence of phosphonium salt (Ph_3PEtI).

Table 1.6. Literature on *N*-alkylation reaction

Sr. No.	Amine	alkylating agent	Catalyst	Time; h	Temp. ^{0}C	Amine Conv.%	(I) sel.;%	(II) sel.,%	Reference
1	Indole	MeI	PEG methyl ether	5	20	60	60	-	Davidson et al.[90a]
2	C_6H_5-NH_2	EtBr	Bu_4NBr / NaOH	2	40	89	55	45	Dehmlow et al.[90b]
4	C_6H_5-NH_2	BnBr	[Bmim] [PF_6]	0.01	60	60	30	70	Chiappe et al. [90c]
5	C_6H_5-NO_2	$HCOOCH_3$	$Ru_3(CO)_{12}$	5	220	99.2	1	99	Jenner & Taleb[91]
6	C_6H_5-NH_2	MeOH	H_2SO_4	6	205	100	1	99	Shreve et al.[92]
7	C_6H_5-NH_2	EtOH	V_2O_5	-	400	35	70	20	Narayanan et al.[93]
8	C_6H_5-NH_2	MeOH	Mg-Al HTlc	6	425	68	100	0	T. Raja et al.[95a]
9	C_6H_5-NH_2	MeOH	Zn-Co-Fe(ZCF2)	1.2	350	74	94	6	Sreekumar et al.[95b]
10	C_6H_5-NH_2	MeOH	ZAPO-5	1.2	350	67	32.5	40	Elangovan et al.[97]
11	C_6H_5-NH_2	MeOH	γ-Al_2O_3	2	425	56	42	51	A-N Ko et al.[99]
12	C_6H_5-NH_2	MeOH	[Zr]ZSM-5	1	400	66.3	78.7	19.8	Park et al.[100]
13	C_6H_5-NH_2	MeOH	Alumina	1	200	96	8	92	Doraiswami et al.[101]
14	C_6H_5-NH_2	MeOH	RHO-zeolite X	1	400	100	10	90	Grace et al.[103]
15	C_6H_5-NH_2	DMC	KY	-	180	99.6	93.5	6.5	Ono et al.[105a]
			NaX or KX		240	100	4.4	95.6	
16	C_6H_5-NH_2	DMC	Mg-Al Htlc	2	275	91	87	13	Jyothi et al.[105c]
17	C_6H_5-NH_2	DMC	CF-5	1	250	60	61	22	Sreekumar et al.[95a]
18	C_6H_5-NH_2	DEC	Hβ	1	200	73.4	71.4	21.4	Yuvaraj et al. [105d]
19	C_6H_5-NH_2	DMC	Na-X	6	300	91	36.6	62	Rao et al.[106]
			Na-EMT			85.4	58.5	41.5	
20	C_6H_5-NH_2	DMC	Na-Y	2.5	90	100	99	1	Tundo et al.[107]
21	C_6H_5-NH_2	DMC	MeI	5	148	100	15	85	Romano et al.[108]
22	C_6H_5-NH_2	DMC	DPAT	2.6	180	99.9	0.3	99.6	Shen & Jiang[109]
23	C_6H_5-NH_2	MeOCOOR	Ph_3PEtI	1	170	99	0	90	Selva et al.[110]

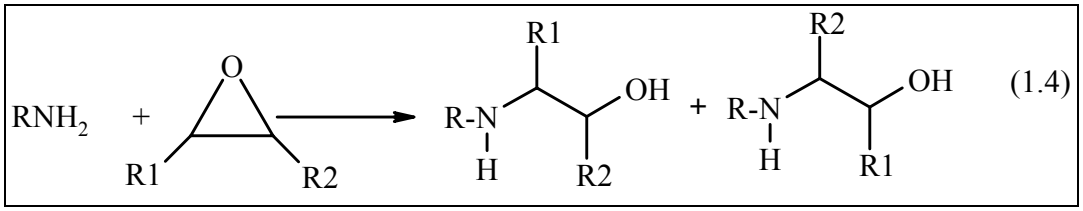
(I)= mono alkylated product; **(II)** = dialkylated product

1.6.2. SYNTHESIS OF β-AMINO ALCOHOLS

β-amino alcohols are an important class of organic compounds due to their bifunctional nature having alcohol and amine functional groups in the same compound, which allows them to react in wide variety of ways.[111] These versatile compounds are extensively used in the medicinal chemistry in the preparation of biologically active natural and synthetic products, artificial amino acids, and chiral auxiliaries for asymmetric synthesis.[112] They are also useful as intermediates in the synthesis of perfumes,[113] dyes, photo developers,[114]and oxazolidones.[115]

1.6.2.1. Synthesis of β-amino alcohols using alkylene oxide

Conventionally β-amino alcohols are produced from alkylene oxide and amines[116] (Equation 1.4).



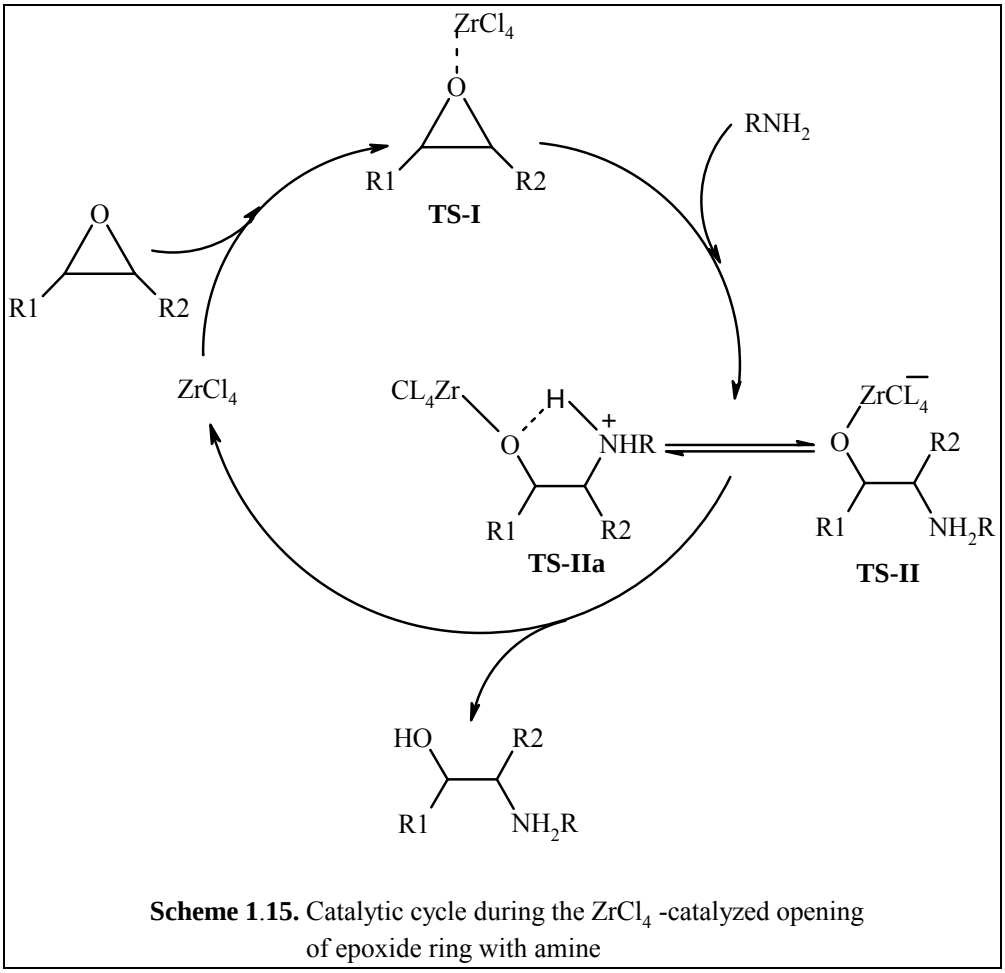
(1.4)

This classical approach, involving heating epoxides with amines works less well with poorly nucleophilic amines such as anilines. Moreover, the lack of appreciable regioselectivity, the requirement for the high temperature (which may pose problem for sensitive epoxides), and the need for an excess of amine in the classical methods of β-amino alcohol synthesis have led to the necessity for activation of the epoxides so as to increase their susceptibility to nucleophilic attack by amines. The various methodologies developed for this purpose include the use of alumina,[117] metal amide,[118] metal halides,[119]

metal alkoxides,[120] metal triflates,[121] alkali metal perchlorates,[122] rare earth metal halides,[123] silica,[124] clays[125] and ionic liquids.[126]

1.6.2.1.1. Mechanism for synthesis of β-amino alcohol

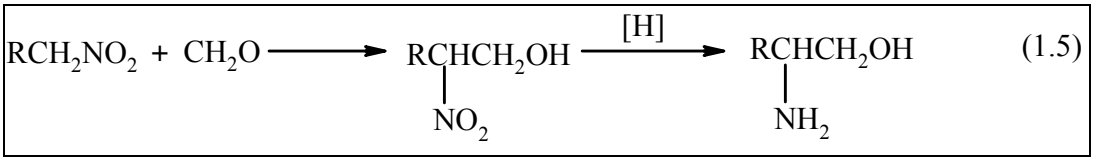
Chakraborti and Kondaskar[112b] have proposed the catalytic mechanism for β-amino alcohol synthesis by $ZrCl_4$ catalyzed ring opening of epoxide with amine (Scheme 1.15). The coordination of Zr_4^+ with the epoxide oxygen (**TS-I**) renders the epoxide susceptible to nucleophilic attack by amine leading to (**TS-II**/**TS-IIa**) followed by protonylisis (via intramolecular proton transfer involving TS-II) to form the amino alcohol. The liberation of the catalyst follows subsequently.



Scheme 1.15. Catalytic cycle during the $ZrCl_4$ -catalyzed opening of epoxide ring with amine

1.6.2.2. Synthesis of β-amino alcohols from nitro paraffins

β-amino alcohols are also synthesized from nitro alcohols by a two steps synthesis (Equation 1.5).[127] In the first step, nitro alcohols are obtained by the condensation of nitro paraffins with aldehydes followed by their reduction to β-amino alcohols in the second step.



(1.5)

The condensation may occur one to three times, depending on the number of hydrogen atoms on the α- carbon of nitro paraffins, giving rise to amino alcohols with one to three hydroxyl groups.

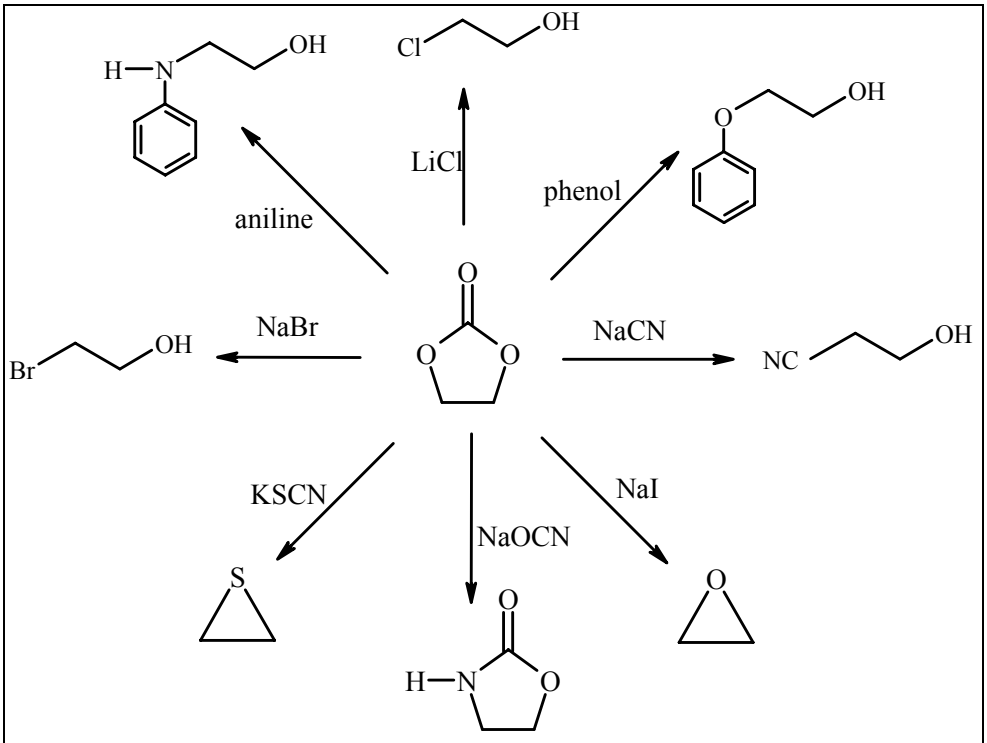
The above mentioned classical routes based on epoxides for the synthesis of β-amino alcohols suffer from the draw back of handling of hazardous epoxides, requires stoichiometric amount of reagents, longer reaction time, high pressure (particularly for ethylene oxide) and temperature conditions. β-amino alcohol synthesis based on nitro paraffins is a multi step synthesis and adverse selectivity towards amino alcohol with one hydroxyl group is the main issue in this route.

In contrast to these, a much safer and attractive synthesis of β-amino alcohol is based on the use of a five-membered alkylene carbonate.

1.6.2.3. Synthesis of β-amino alcohols using alkylene carbonate

From the industrial point of view, alkylene carbonates are important precursors. In particular, ethylene carbonate (EC) and propylene carbonate (PC) have been commercially produced through benign routes and are available for over 45 years.[128, 129]

These compounds have significant physical properties such as high boiling and flash point, low odor levels and evaporation rates, low toxicity and high solvency besides being to biodegradabe. Being versatile, these compounds have found numerous applications both as solvents and reactive intermediates (Scheme 1.16).[33b]

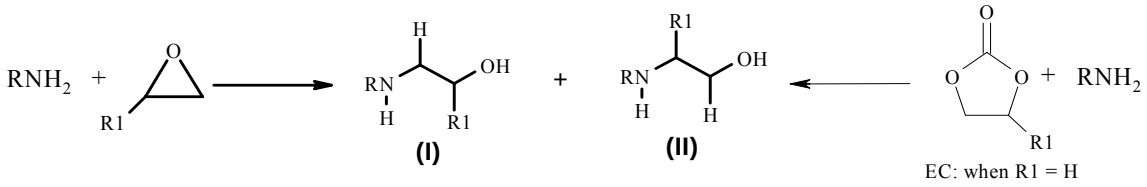


Scheme 1.16. Applications of alkylene carbonate as useful synthons

Among all these organic transformations using alkylene carbonates, synthesis of β-amino alcohol is an important transformation. *N*-alkylation employing alkylene carbonate is a simple reaction, easy to handle and does not require high pressure setup.

Though, it is a simple and useful reaction, it is not well investigated. Gulbins and Hamann (1966) have reported the reaction of aromatic amine with alkylene carbonate in presence of LiCl catalyst to give oxazolidones as major products, along with β-amino alcohol.[130] Kaye et al.[131] reported the synthesis of *N*-methyl *N*-phenyl ethanolamine from *N*-methyl aniline and ethylene carbonate using lithium amide catalyst. It has also been reported that the reaction between aliphatic amines and alkylene carbonate gives polymeric products possessing carbamate and carbonate functionality.[132] A process for the alkoxylation of an active hydrogen-containing compounds with an alkylene carbonate in the presence of mixed metal oxide to give low yield of β-amino alcohol has been patented by King.[133]

Table 1.7. Literature on β-amino alcohol synthesis



Sr. No.	Amine	alkylating agent	Catalyst	Time; h	Temp. ^{0}C	Amine Conv.%	(I) sel.;%	(II) sel.,%	Reference
1	C_6H_5-NH_2	PO SO	$ZrCl_4$	0.25	25	100 98	100 2	- 98	Chakraborti et al[112b]
2	C_6H_5-NH_2	CyO	Al_2O_3	0.16	40	69	100		Posner et al.[117]
3	C_6H_5-CH_2NH_2	CyO	$LiNH_2$	24	25	100	70		Kissel et al.[118a]
4	C_6H_5-NH_2	CyO	$(Et)_2AlNH_2$	2-3	25	52	100		Overmann et al.[118b]
5	C_6H_5-NH_2	SO	$CoCl_2$	3	25	98	5	95	Sundararajan[119a]
6	C_6H_5-NH_2	CyO	$TaCl_5$-silica gel	-	25	100	85	-	Chandrashekhar et al.[119c]
7	C_6H_5-NH_2	CyO	$Cu(OTf)_2$ $Sn(OTf)_2$	20-30	25	100 100	95 94	-	Sekar et al.[119b]
8	C_6H_5-NH_2 C_4H_9-NH_2	CyO PO	$LiClO_4$	38 2	25	100 100	98 40	0 60	Chini et al.[121]
9	C_4H_9-N	SO CyO	Montmorillonite	3	70	-	17.5 46	32.5	Mojtahedi et al.[125]
10	C_6H_5-NH_2	SO CyO	$[Bmim]BF_4$	5 6	25	- -	- 83	85 -	Yadav et al.[126]
11	C_6H_5-NH_2	EC	LiCl	5	176	100	18		Gulbins et al.[130]
12	C_6H_5-NH(Me)	EC	$LiNH_2$	4	145-190	53.5	53.5		Kaye et al.[131]

PO: propylene oxide; SO: styrene oxide; CyO: cyclohexene oxide; EC: ethylene carbonate; *CyO & EC gave single product

1.7. SCOPE AND OBJECTIVES OF THESIS

In the light of growing public and political awareness of chemical industry polluting the environment, chemist have been contributing significantly to improve the existing chemical routes and develop new routes that are less damaging to the ecosystem. In the manufacturing processes of fine chemicals, stoichiometric amount of reagents and homogeneous acid and bases of Brønsted and Lewis catalysts are still applied to a great extent in the liquid phase which produces a lot of unavoidable side products and inorganic salts that causes a lot of burden on eco-system. In particular, an underdeveloped area of fine chemicals is in the replacement of traditional catalysts and reagents which are corrosive, toxic, produced by eco-unfriendly processes and which produce inorganic salts that are expensive to dispose. Some of the examples of undesirable reagents used for carboxylation and alkylation are phosgene, methyl halides and dimethyl sulfate (DMS).

In this context the aim of present work was to develop more efficient and more selective catalyst systems as well as the development and rationalization of new greener routes for the synthesis of fine chemicals using organic carbonates as benign reagents. Organic carbonates such as dimethyl carbonate, ethylene carbonate etc. are non-toxic, biodegradable and produced commercially via benign routes. The use of carbonates thus can replace potentially hazardous routes that uses phosgene and DMS to produce fine chemicals such as carbamates, *N*,*N*-dialkyl anilines and β-amino alcohols which have wide range of applications in pharmaceuticals, agriculture industry and polymer industries.

With these objectives, the following specific reactions have been studied.

- Carbamate synthesis via transfunctionalization of substituted ureas and carbonates
- Selective synthesis of *N*,*N*-dimethyl anilines from aromatic amines and dimethyl carbonate
- Synthesis of β-amino alcohols from aromatic amines and alkylene carbonates
- Selective tandem synthesis of β-amino alcohols from aromatic amines, dialkyl carbonates and ethylene glycol
- Kinetic and mechanistic study of *N*-alkylation of aniline by ethylene carbonate to β-amino alcohols in presence of Na-Y zeolite as catalyst

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Chapter 2

Carbamate Synthesis via Transfunctionalization of Substituted Urea and Organic Carbonate

2.1. INTRODUCTION

Carbamates are compounds of growing interest because of their wide applications in agriculture industry as herbicides, fungicides and pesticides,[1] in pharmaceutical industries as drug intermediates and in polymer industries, in the synthesis of polyurethanes.[2] They are also useful as protecting groups in organic synthesis, particularly, in peptide synthesis.[3] The conventional production of carbamate is almost exclusively based on phosgene technology.[4] This process besides being highly energy intensive uses highly corrosive and toxic phosgene gas and produces stoichiometric quantities of hydrochloric acid as a side product and contamination of the remaining chlorine anion to final product. Furthermore, HCl causes serious corrosion, and a stoichiometric amount of NaOH is required to neutralize the HCl. Several efforts have been made towards the development of environmentally friendly routes using non-toxic reagents for preparation of carbamate such as, reductive carbonylation of nitro aromatics,[5] oxidative carbonylation of amines,[6] carboxylation of amine using CO_2[7]or organic carbonate[8] and alcoholysis of urea.[9] However, synthesis of carbamate by reductive carbonylation of nitro compounds suffers from a lack of economic viability as it utilizes only one-third of CO and there exist difficulty in separation of CO with CO_2. In oxidative carbonylation process, although CO can be utilized effectively, the formation of water lowers the atom utility of the reactants. In addition, the operational safety resulting from oxygen in combination with CO must be considered. These two processes required severe reaction conditions such as high temperature and pressure, and a noble metal catalyst such as Pd or Ru for the carbonylation reactions whose recycle and recovery is difficult. Carbamate synthesis by amine carboxylation using clean and safe carboxylating

reagent such as CO_2, which is an attractive route for research workers, but at present this method is not attractive for bulk production because it utilizes stoichiometric amount of alkyl halides and inorganic bases, that generates metal halides as a side products brings about an increase in the *E-factor*. Synthesis of carbamate using organic carbonate or urea as reagents results in poor atom economy and in each case alcohol or amine is produced as a byproduct reducing the functional group efficiency of the reagent (for detail see Section 1.5.2.4 and 1.5.2.5). Two useful measures of the environmental impact of chemical process[10] are the *E-factor*, defined by the mass ratio of waste to desired product, and the *atom-economy* (atom utilization) calculated by dividing the molecular weight of the desired product by the sum of the molecular weight of all substances produced in the stoichiometric equation.

In view of this, objective of the present work was to develop a new environmentally benign route for carbamate synthesis. This new route comprises of transfunctionalization of substituted ureas and organic carbonates for carbamate synthesis. In this chapter, experimental results on carbamate synthesis using homogeneous as well as heterogeneous catalysts are presented. Various aspects such as, catalytic activity, catalyst recycles, and reactivity of various substituted ureas and organic carbonates have been studied. In the present work, the effect of process parameters on the synthesis of methyl *N*-methyl carbamate (MMC) has been investigated. A reaction mechanism has been postulated explaining the role of n-dibutyl tin oxide catalyst in the carbamate synthesis. Various carbamates were synthesized by this route, and were isolated and fully characterized by elemental analysis, ^{1}H, ^{13}C NMR, IR and GC-MS.

2.2. EXPERIMENTAL SECTION

2.2.1. MATERIALS

Substituted anilines, dimethyl carbonate (DMC), diethyl carbonate (DEC), $FeCl_3$, $AlCl_3$, $Mg(NO_3)_2$, NaOH, $NaHCO_3$ were purchased from S.D. fine chemical ltd. India, and used as such. Diphenyl carbonate, catalyst precursors $Ti(IV)(O)(acac)_2$, $Cu(acac)_2$, $Al(NO_3)_3$, $PbZrO_3$, $SnCl_4(H_2O)_6$, Bu_2SnO (DBTO) and silica gel (davisil) were purchased from Aldrich, USA and used as received. Silica gel was purchased from W.R. grace, USA. Substituted ureas,[11] n-dibutyl carbonate[12] and unsymmetrical methyl phenyl carbonate[13] were synthesized by reported procedures and used after purification. $Bu_2Sn(OPh)_2$[14] and Mg-Al Htlc[15] were prepared according to literature procedure.

2.2.1.1. General procedure for the preparation of disubstituted ureas[11]

An aromatic amine (620 mmol) was mixed with urea (300 mmol) in a 100 ml two-necked round bottom flask. A magnetic needle was placed in it for stirring the reaction mixture. The flask was fitted with a refluxing water condenser. N_2 gas was purged through the reaction mixture to drive away ammonia formed; rate of purging was approximately 1 ml/min. The reaction mixture was heated with constant stirring at 423 K for 8–12 h. The reaction was monitored by ammonia evolution, which was checked by litmus paper. The driving force for this reaction is efficient ammonia removal.

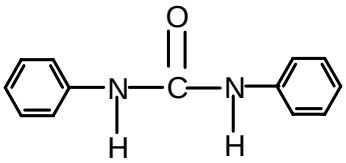
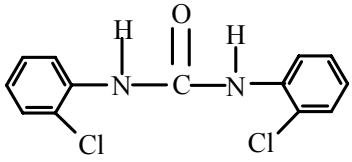
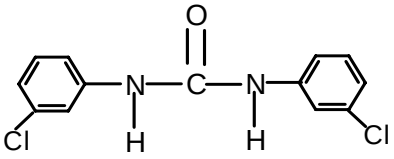
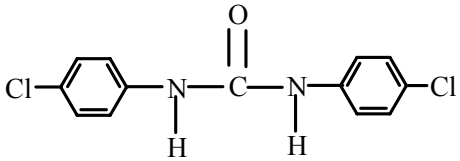
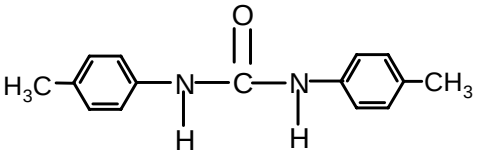
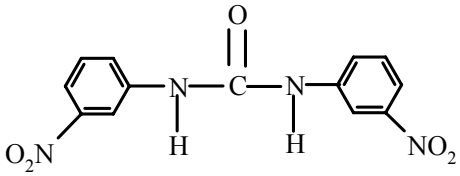
After completion of the reaction, the reaction mixture was cooled to room temperature and filtered. Solid was first washed with excess of water to remove the unreacted urea then with hot water to remove the mono substituted urea, which was formed in the trace amount. Then this solid was washed with organic solvents like pet

ether, chloroform etc. to remove excess of unreacted amine. The recovered crystalline solid material was recrystallized from water-ethanol. The yield of the product was more than 98% for all the substituted ureas synthesized. The products were confirmed by elemental microanalysis and I.R. spectroscopy (Table 2.1).

2.2.1.2. Synthesis of dibutyl carbonate[12]

The reaction was carried out in 100 ml two neck round bottom flask, equipped with a dropping funnel and fractionating column. n-butanol (200 mmol) was added followed by di-n-dibutyl tin oxide (2 mmol) and the mixture was heated to 393 K. When the catalyst completely dissolved in butanol, dimethyl carbonate (230 mmol) was added drop wise to the reaction mixture over the period of 0.5 h. The pot temperature was between 383 and 393 K after complete addition of DMC. The occurrence of reaction was indicated by attainment of temperature of 335-336 K at the top of the column, which corresponds to the 70:30 constant boiling azeotrope of methanol and DMC. This azeotrope was collected slowly in the receiver flask. The pot temperature was gradually increased from 393-453 K. When the azeotrope had completely distilled out, the pot temperature was raised to 493 K to enable removal of excess DMC. After completion of the reaction, the product dibutyl carbonate (16 g) was isolated in pure form by distillation under reduced pressure and was confirmed by GC-MS analysis.

Table 2.1. Synthesis of disubstituted urea

Sr. No.	Amine	Structure	ν_{CO} cm^{-1} (In KBr)	Elemental analysis %
1	Aniline	 *N,N'*- diphenyl urea	1648	C: 73.7 H: 5.84 N: 13.4
2	*o*- chloro aniline	 *N,N'*-bis (2-Cl-phenyl) urea		C: 55.3 H: 3.97 N: 10.3 Cl: 25.1
3	*m*- chloro aniline	 *N,N'*- bis (3-Cl-phenyl) urea	1635	C: 55.8 H: 3.92 N: 10.1 Cl: 25.6
4	*p*- chloro aniline	 *N,N'*- bis (4-Cl- phenyl) urea		C: 55.9 H: 3.94 N: 10.2 Cl: 25.3
5	*p*-Toludine	 *NN'* - bis (4-CH_3 phenyl) urea	1640	C: 75.1 H: 6.45 N: 11.8
6	*m*- nitro aniline	 *NN'*- bis (3- NO_2 phenyl) urea	1630	C: 51.5 H: 3.81 N: 18.2

2.2.1.3. Synthesis of methyl phenyl carbonate[13]

Methyl phenyl carbonate was prepared by disproportionating transesterification of dimethyl carbonate and diphenyl carbonate. In a typical reaction, dimethyl carbonate (0.12 mol), diphenyl carbonate (60 mmol) and n-dibutyl tin oxide (1 mmol) were charged to the parr autoclave of 50 ml capacity. The contents were flushed with nitrogen and autoclave was pressurized with nitrogen (3.4 MPa). Then reaction was carried out at 423 K for 5 h. After completion of the reaction, methyl phenyl carbonate (5.5 g) was isolated by distillation under reduced pressure and was confirmed by GC-MS analysis.

2.2.1.4. Synthesis of $Bu_2Sn(OPh)_2$[14]

Bu_2SnO (10 mmol) and diphenyl carbonate (10 mmol) were charged in to a round bottom flask equipped with magnetic stirrer and condenser. The reaction mixture was heated at 353 K in preheated oil bath and the temperature was then raised in steps up to 413 K. At 413 K, a rapid evolution of CO_2 began and after complete evolution of CO_2, reaction was stopped. A clear liquid of $Bu_2Sn(OPh)_2$ was obtained and which was characterized by IR.

2.2.1.5. Preparation of Mg-Al hydrotalcite (Mg/Al = 3) [15]

Solution-A containing aluminium nitrate nonahydrate (20 mmol) and magnesium nitrate hexahydrate (60 mmol) dissolved in 100 ml of double distilled water and solution-B containing sodium hydroxide (160 mmol) and sodium carbonate (16 mmol) dissolved in 100 ml of double distilled water were prepared. Both the solutions were added simultaneously dropwise into a 1000 ml beaker containing 100 ml of distilled water with

vigorous stirring for 0.5 – 0.75 h and pH of the solution was maintained in the range of 9 – 10. After completion of addition, the mixture was kept for ageing at 338 K for 18 h. Then solid mass was filtered and more washings of distilled water were given unless it was free from alkali. After that, white solid was dried at 393 K for 24 h. X-ray diffraction analysis of the product showed the peaks corresponding to (003), (006), (110) and (113) planes that were characteristic of clay mineral (hydrotalcite) having layered structure (Figure2.1).[15]

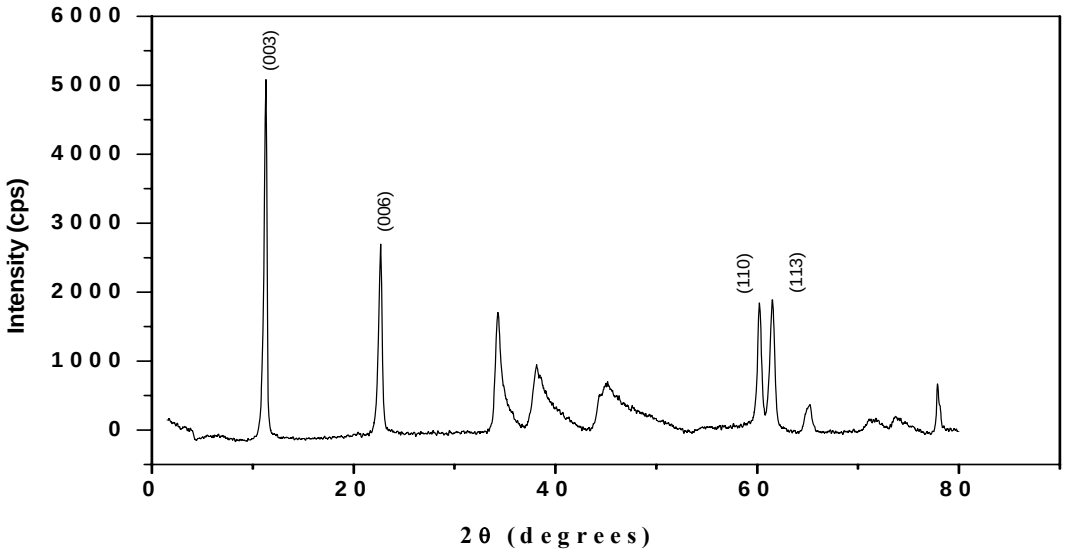


Figure 2.1. XRD pattern of Mg-Al Hydrotalcite

2.2.2. GENERAL PROCEDURE FOR CARBAMATE SYNTHESIS

In a typical experimental procedure, known quantities of substituted urea, organic carbonate and catalyst were charged to a dried round bottom flask (50 ml) equipped with temperature controller, a stirrer and reflux condenser. The contents were flushed few times with nitrogen and heated to desired temperature into a preheated oil bath. The reaction was continued for the specified time. After the reaction, reaction mixture was

cooled to room temperature and carbamate was separated by column chromatography using silica gel as a solid stationary phase and ethyl acetate: chloroform mixture in proportion 0.2:9.8 as eluent.

Carbamate synthesis reactions using low boiler dialkyl carbonates were carried out in a 50 ml Parr Autoclave made of Hastelloy-C-276 having facilities for gas inlet, outlet, intermediate sampling, temperature controlled heating and variable agitation speed (Figure 2.2). As a safety precaution, a rupture disc (gold faced), which can withstand a maximum of 14 MPa pressure, was also fitted in the reactor.

Figure 2.2. Parr autoclave

In a typical experiment, required amounts of the catalyst, substituted urea and dialkyl carbonate were charged into the reactor. The reactor was purged with nitrogen several times and then pressurized with nitrogen up to 3.4 MPa. Then the contents were heated to the required temperature and the progress of the reaction was monitored by

withdrawing the intermediate samples which were quantitatively analyzed by GC for reactants and products. The reaction was continued for specified time, the contents cooled to room temperature and the gas vented off. Details of the liquid phase analysis are given in the section 2.2.3. The products were further confirmed by GC-MS, NMR and IR analysis. Spectral data of all the carbamates prepared are given in the section Spectra.

2.2.3. ANALYTICAL METHODS

IR spectra were obtained using a Perkin Elmer Spectrum-2000 in transmission mode using KBr pellets. NMR was obtained from a Brucker-Av-200, Brucker-MSL-300 and Brucker-DRX-500 machines. Elemental analysis of the complexes was carried out on a CHNS-O EA1108, Elemental analyzer of Carlo Erba Instruments, Italy. Liquid samples were analyzed on a Hewlett Packard 6890 Series GC equipped with auto sampler instrument, controlled by the HP Chemstation software, and using an HP-5 capillary column (30 m x 320 μm x 0.25 μm film thickness, on a 5% phenyl methyl siloxane stationary phase). GC-MS was carried out on Agilent 6890 instrument employing earlier standardized GC method. The standard conditions for GC analysis are given in Table 2.2.

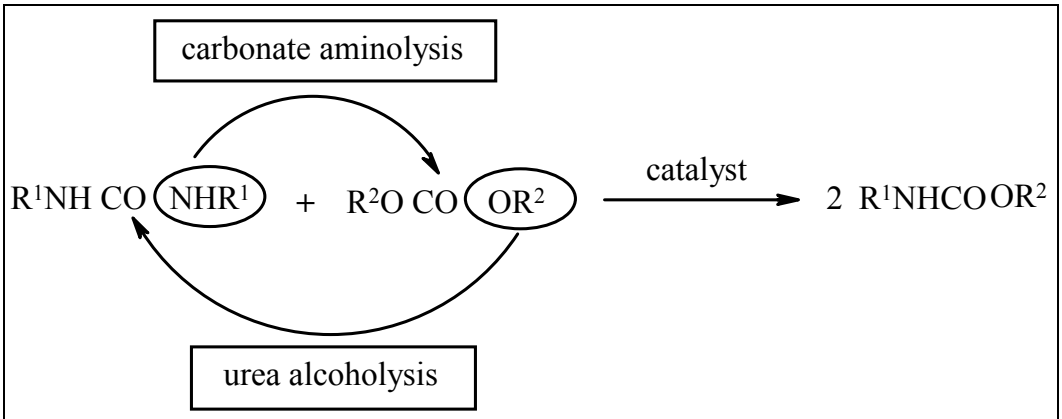
Table 2.2. Standard conditions for GC analysis

Parameters	Conditions
Injector (split) temperature	523 K
Flame ionization detector (FID) temperature	573 K
Column temperature (HP-5 capillary column)	313 K–563 K (programmed)
Inlet Pressure (He)	20 psig
Carrier gas (He) flow rate	2 ml/min
Split ratio	25:1

2.3. RESULTS AND DISCUSSION

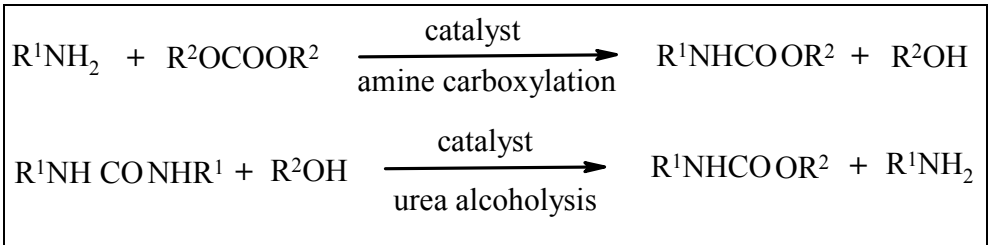
2.3.1. CARBAMATE SYNTHESIS USING HOMOGENEOUS CATALYST

In this work, reaction of substituted urea and organic carbonate for carbamate synthesis has been investigated using homogeneous catalysts (Scheme 2.1). In this reaction, aminolysis of organic carbonate and alcoholysis of urea is occurring in tandem manner.



Scheme 2.1:

With this route, 100% atom economy was achieved where as amine carboxylation and urea alcoholysis reactions showed poor atom economy by loss of alcohol and amine functionality respectively (Scheme 2.2).

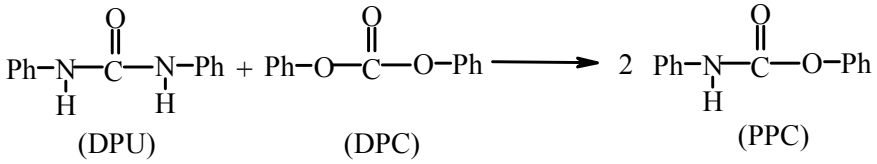


Scheme 2.2:

2.3.1.1. Preliminary experiments for catalyst screening

Various homogeneous catalysts were screened for carbamate synthesis, which were well known for amine carboxylation and urea alcoholysis reactions. For this purpose, reactions were carried out employing *N,N'*-diphenyl urea (DPU) and diphenyl carbonate (DPC) as substrates for synthesis of phenyl *N*-phenyl carbamate (PPC) as a model reaction. The results on catalysts screening for PPC synthesis are presented in Table 2.3.

Table 2.3. Catalyst screening for synthesis of phenyl *N*-phenyl carbamate



(DPU) (DPC) (PPC)

Ph: phenyl

Entry	Catalyst	Time, (h)	Yield (%)
1	none	24	traces
2	$Ti(IV)(O)(acac)_2$	15	34
3	$Cu(acac)_2$	4	71
4	PPh_3	4	25
5	NaOH	4	32
6	PhONa	4	56
7	$(C_2H_5)_4NBr$	4	81
8	$FeCl_3$	4	16
9	$AlCl_3$	4	22
10	$SnCl_4(H_2O)_6$	4	11
11	$Bu_2Sn(OPh)_2$	4	20
12	Bu_2SnO	4	93

Reaction conditions: DPU, 3.16 mmol; DPC, 15.6 mmol; catalyst, 0.89 mmol; T, 423 K; Agitation speed, 16.7 Hz; N_2 atmosphere

From the catalyst screening it was observed that a non-catalytic reaction between DPU and DPC produced only traces of PPC after 24 h indicating that catalyst was essential for formation of PPC (Table 2.3, entry 1). Urea alcoholysis catalysts such as titanium and copper acetyl acetonate complexes[9d] were also screened (see entry 2, 3) and copper catalyst was found to be having good activity. Classical Lewis acid catalysts[8e-h] such as $FeCl_3$, $AlCl_3$, $SnCl_4$, (see entry 8-10) known for amine carboxylation reactions showed poor activity compared to basic catalysts such NaOH, phenolate ion, onium salts (see entry 5-7). Organotin complexes were also screened, which were known to be excellent transesterification catalysts for carbonates and esters.[12b] Several organotin complexes were employed for synthesis of carbamate from DPU and DPC in which acidity of catalyst was varied to highly acidic to mild basic tin catalysts. The results of these experiments showed that basic tin complexes such as dibutyl tin oxides (DBTO) gave excellent carbamate yield (entry 12) compared to acidic tin compounds such as $SnCl_4$ ($6H_2O$) (entry 10), while, $Bu_2Sn(OPh)_2$ having intermediate acidity showed moderate yields of PPC (entry 11). Therefore, further reactions with various ureas and carbonates were carried out using DBTO as a catalyst.

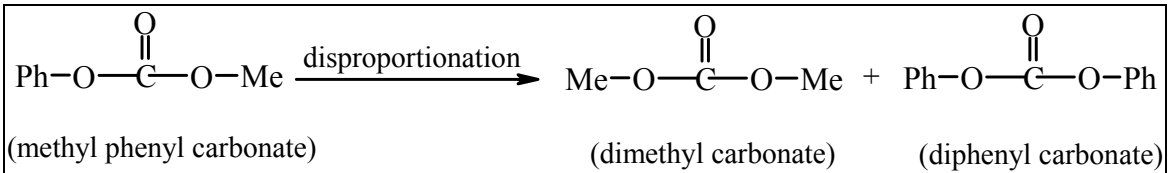
2.3.1.2. Reactivity of substituted urea and carbonate towards carbamate formation

The reaction between substituted urea and carbonate to form carbamate is a new reaction and literature on the reactivity pattern of ureas and carbonate towards carbamate formation is not available. However, considerable amount of work on ester aminolysis of carbonates and alcoholysis of substituted ureas has been reported in literature (and discussed later) which will be useful in understanding the reactivity behavior observed for carbamate synthesis from urea and carbonate.

Ester aminolysis of substituted diphenyl carbonates to carbamate have been investigated in detail.[16] According to these investigators the reaction between organic carbonate and amine is a function of basicity of amine. It is well known that in ester aminolysis of substituted carbonates, the reaction depends upon the basicity of attacking amine. It is generally belived that aminolysis proceeds smoothly when pK_a values of attacking amines are about 4-5 units higher than that of the leaving group (e.g. alkoxides or aryloxide).[17] The reactivity of carbonate depends upon the electrophilicity of carbonyl carbon; the factors that help increase the electrophilicity of carbonyl carbon will increase the rate of reaction. An electron withdrawing substituents on phenoxide or alkoxide will facilitate nucleophilic attack (retarded by electron donating substituents).[18] However, the final reactivity will depend on the pK_a of attacking amine as noted earlier. Similarly, alcoholysis of substituted urea was accelerated by electron donating group on alcohol and slowed by electron withdrawing groups, provided that hindrance factor was not coming into play.[9d] On the other hand, electron-donating substituents on phenyl urea increased the reactivity of urea, while the electron attracting substituents on aryl group decreased reactivity of urea. [19]

A few substituted ureas were reacted with diphenyl carbonate using DBTO as a catalyst and these results are summarized in Table 2.4. It was observed that substituted diphenyl urea having electron withdrawing (entry 2-5) or donating (entry 6) groups presents on the aromatic ring did not show any prominent electronic effect on their reactivity towards diphenyl carbonate and these ureas gave excellent yields of carbamate. Except, that for sterically hindered *N,N`*-bis(2-chloro phenyl) urea which showed substantially low carbamate yield (Table 2.4, entry 2). While carbonate reactivity towards

diphenyl urea seemed to be following the rule that carbonate reactivity increased with leaving group ability of phenoxide and alkoxides (see entry 1 & 7), which was consistent with the trend observed in aminolysis of carbonates.[16a] The reactivity of alkyl carbonates towards ureas was found to decrease in the order, dimethyl carbonate> diethyl carbonate > dibutyl carbonate (entry 7-11). This observed reactivity of carbonate suggested that carbonyl carbon of dimethyl carbonate was most electrophilic center and that of dibutyl carbonate was least in the three carbonates investigated. A similar kind of reactivity was earlier observed for alcohols in transesterification of DMC and was attributed to the steric factors rather than electronic effect of various alcohols. [12b,20]



Scheme 2.3

When unsymmetrical carbonate such as methyl phenyl carbonate was reacted with DPU, phenyl *N*-phenyl carbamate and methyl *N*-phenyl carbamate (MPC) were formed in 62% and 10% yields respectively (Table 2.4, entry 12). However, as per the stoichiometry of reaction (Scheme 2.3) equal amount of carbamates should have been formed. It is well known that disproportionation of methyl phenyl carbonate to DPC and DMC is likely to occur under the catalytic conditions (Scheme 2.3).[21] Analysis of reaction crude also confirmed the formation of symmetrical carbonates from methyl phenyl carbonate. The symmetrical carbonates thus formed reacted independently with DPU to form corresponding carbamates and yields of carbamates depended upon the reactivity of carbonates viz, DPC and DMC. Higher yields of methyl *N*-phenyl carbamate

were obtained as DPC is more reactive than DMC. The reactivity pattern study showed a general behavior in that excellent carbamate yields were obtained when an aromatic (or aliphatic) urea was reacted with aromatic (or aliphatic) carbonate but poor yields were envisaged when aromatic urea was reacted with aliphatic carbonate and vice versa.

Table 2.4. Synthesis of carbamates using dibutyl tin oxide catalyst

$R^1NH\,CO\,NHR^1 + R^2OCOOR^2 \longrightarrow 2\ R^1NHCO\,OR^2$

Entry	R^1 (urea)	R^2 (carbonate)	Time, (h)	Product code	Isolated Yield (%)
1	C_6H_5	C_6H_5	4	**1a**	93
2	2-Cl-C_6H_4	C_6H_5	4	**1b**	75[a]
3	3-Cl-C_6H_4	C_6H_5	4	**1c**	92
4	4-Cl-C_6H_4	C_6H_5	4	**1d**	90
5	3-$NO_2C_6H_4$	C_6H_5	4	**1e**	89
6	4-CH_3-C_6H_5	C_6H_5	4	**1f**	90
7[b]	C_6H_5	CH_3	4	**2a**	77
8[b]	C_6H_5	C_2H_5	4	**2b**	61
9[b]	C_6H_5	C_4H_9	4	**2c**	50
10[b]	CH_3	CH_3	4	**3a**	91
11[b]	CH_3	C_2H_5	4	**3b**	64
12[c]	C_6H_5	-	15	-	72

Reaction conditions: substituted urea, 3.16 mmol; carbonate, 15.6 mmol; catalyst, 0.89 mmol; T, 423 K; Agitation speed, 16.7 Hz; N_2 atmosphere; [a]carbamate are unstable [b]reactions were carried out in a 50 ml autoclave using 17ml of carbonate and under nitrogen pressure of 3.4 MPa; [c]reaction was carried out using methyl phenyl carbonate

2.3.1.3. Synthesis of methyl *N*-methyl carbamate (MMC)

Methyl *N*-methyl carbamate (MMC) an industrially important carbamate was synthesized by reacting *N*,*N*'-dimethyl urea (DMU) with dimethyl carbonate (DMC). Various process parameters such as, effects of DBTO concentration, DMU concentration, DMC concentration and temperature were studied for MMC synthesis with the aim to understand the kinetics and mechanism of the reaction. For this purpose, few initial experiments were carried out to examine the material balance (for side product formation etc.) as well as the contribution of non-catalytic reaction in the formation of methyl *N*-methyl carbamate from *N*,*N*'-dimethyl urea and dimethyl carbonate. Figure 2.3 shows a typical concentration-time profile in a high-pressure batch reactor. In this Figure since DMC acted as a solvent as well as the reactants, DMU was considered as limiting reactant. Hence, on the basis of moles of DMU reacted carbamate formation and DMC consumed were tallied. Conversion of DMU was increased with respect to time and correspondingly DMC was also consumed with concurrent formation of MMC, indicating no side products formation and material balance was in complete agreement with the stoichiometry. It was observed that there was 91% DMU conversion with 100% selectivity for MMC formation at the end of six hours, this also showed that the reaction was thermodynamically favorable under the experimental conditions. It may be noted that Figure 2.3 shows an induction period of about 45 minutes at this temperature and indicated the formation of an active catalytic species from catalyst precursor DBTO that was responsible for the catalytic reaction. Fu and Ono have also reported similar observation earlier for PbO catalyzed methoxy carbonylation of aniline with dimethyl carbonate to carbamate.[8f]

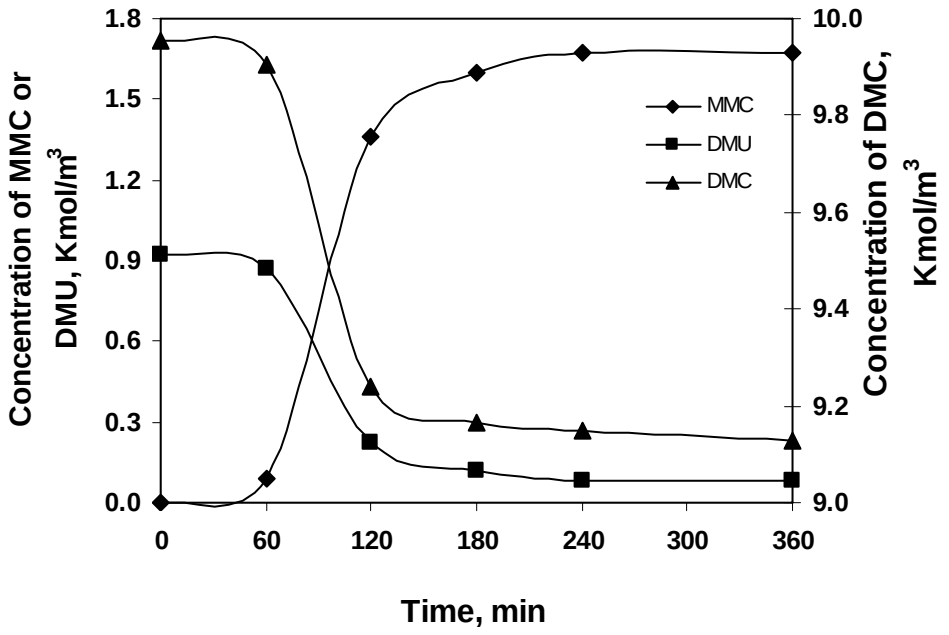


Figure 2.3 Concentration -Time profile of MMC synthesis

Reaction conditions: DMU, 0.92 Kmol/m^3; DMC, 9.95 Kmol/m^3; DBTO, 0.06 Kmol/m^3; T, 423 K; Time, 6 h; N_2 pressure, 3.4 MPa; Agitation speed, 16.7 Hz; Total volume, 30 ml.

2.3.1.3.1. Effectiveness of DBTO as catalyst

Since, a base can effectively catalyze the reaction between urea and carbonate and aliphatic ureas have mild basicity, we explored the possibility of a non-catalytic reaction between and aliphatic carbonate. For this purpose, non-catalytic reaction between *N*,*N*-dimethyl urea (DMU) and dimethyl carbonate (DMC) was investigated and these results are presented in Table 2.5. The results of non catalytic reaction between urea and carbonate showed that, basic urea such as *N*,*N*`-dimethyl urea activated carbonate, which gave methyl *N*-methyl carbamate in good yields even in the absence of any catalyst (37%; Table 2.5, entry 1).

Table 2.5. Effect of catalytic conditions on MMC synthesis

Entry	Conditions	Pressure, MPa	Yields[a] of MMC, %	MMC yield due to DBTO, %
1	Non catalytic	Autogenous	37	-
2	Non catalytic	3.4; N_2	65	-
3	DBTO	Autogenous	91	54 (91-37)
4	Non catalytic	3.4; CO_2	9	-
5	DBTO	3.4; CO_2	62	53 (62-9)

Reaction conditions: DMU, 15.34 mmol; DMC,169.2 mmol; DBTO, 1.81 mmol; T, 423 K; Time, 4 h; Agitation speed, 16.7 Hz; reaction volume, 17 ml; [a] GC yields.

On the other hand less basic urea like *N,N'*- diphenyl urea needs catalyst for carbamate formation from diphenyl carbonate (Table 2.3, entry 1). Thus, catalysis is also dependent on acidity and basicity of substrates as well as catalyst. In order to further confirm that urea having basic property which catalyzes carbamate synthesis reaction of carbonate and urea, an experiment was performed with carbon dioxide with the aim to neutralize the basic sites of substituted urea resulting in lower activity. As expected, this experiment gave very poor yields of MMC (9% yields, Table 2.5, entry 4). Thus, carbon dioxide deactivated urea and thereby decreased its ability to activate dimethyl carbonate. This confirmed our reasoning that DMU basicity was playing a key role in non-catalytic reaction between DMU and DMC and that, DMU was acting as a both reactant as well as a catalyst. However, the results obtained on the effect of pressure of inert gas such as nitrogen on non-catalytic reaction between DMU and DMC was most unexpected. At 3.4 MPa pressure of nitrogen, the MMC yield increased to about 65% (entry 2).

Experiments were also undertaken to understand the effect of CO_2 on DBTO activity, and the results are also shown in Table 2.5. Since MMC was also formed via a non-catalytic route (entry 1 and 2) activity due to DBTO alone could be calculated by accounting for the contribution due to non-catalytic reaction. Entry 3 in Table 2.5. showed that overall yield of MMC obtained under DBTO catalyzed reaction conditions was 91%, which included 37% yield of MMC due to non-catalytic reaction (entry 1, yields in absence of DBTO) and the rest 54% yields was thus due to DBTO. While, in the presence of CO_2, DBTO catalyzed reaction showed 62% of MMC yield (entry 5) and under CO_2 atmosphere only 9% MMC was formed due to non-catalytic reaction (entry 4). It indicated that even in the presence of CO_2, MMC yield due to DBTO was not affected (compare entry 3, and 5 for MMC yields due to DBTO). Therefore, it was concluded that most of catalytic activity of DBTO was retained even under CO_2 atmosphere.

2.3.1.3.2. Effect of DBTO concentration on MMC synthesis

Effect of DBTO concentration on conversion and selectivity behaviors in MMC synthesis was investigated in the range of 0.026 – 0.16 Kmol/m^3. A plot of MMC yields Vs catalyst concentration showed that with increased catalyst concentration, MMC yield increased, showing first order dependence normally observed for catalyst concentration effect. Except at high DBTO catalyst loading, the rates seemed to be tapering off with catalyst loading (Figure 2.4). In the present case, both the reactants (urea and carbonate) and catalyst were infinitely soluble in toluene under reaction conditions offering a homogeneous liquid phase and therefore no liquid side mass transfer resistance was expected. However, it may be noted that in absence of catalyst appreciable amount of non-catalytic reaction was also contributing to MMC yield, indicating that contribution of

catalysis was not very significant for the reaction. Thus catalyst loading effect showed a first order dependence on rate up to 0.107 Kmol/m^3 DBTO concentration and beyond that showed less than first order dependence with increased catalyst concentration.

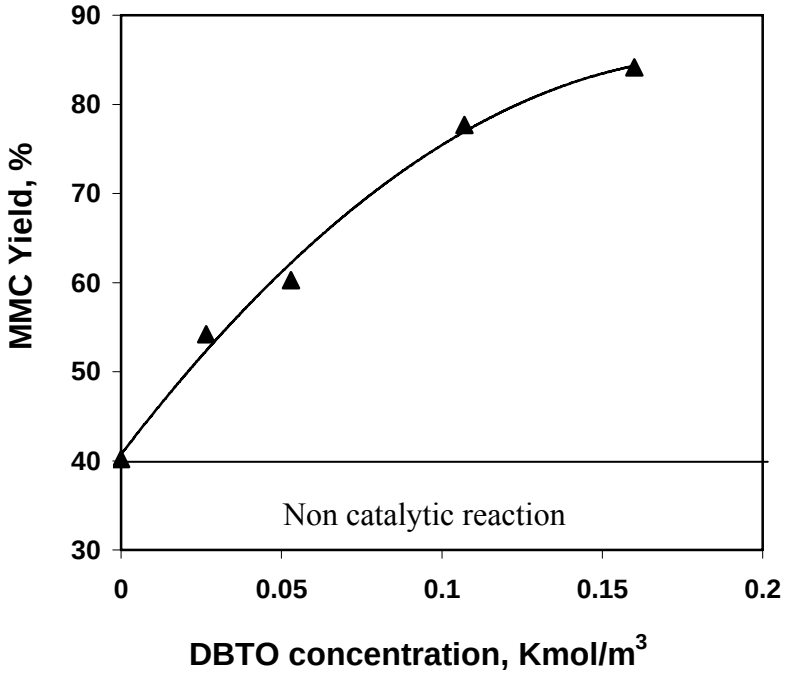


Figure 2.4. Effect of DBTO catalyst loading on MMC yield

Reaction conditions: DMU, 15.3 mmol; DMC, 55.56 mmol; T, 423 K; Time, 4 h; N_2 pressure, 3.4 MPa; Agitation speed, 16.7 Hz; Solvent, Toluene; Total volume, 17ml.

2.3.1.3.3. Effect of DMU concentration on MMC synthesis

The effect of DMU concentration on yield of MMC was investigated in the concentration range of 0.45-1.82 Kmol/m^3 and the results are presented in Figure 2.5. The DMU concentration effect showed that increased concentration of DMU increased the MMC production showing a positive effect of DMU concentration. While, MMC yield and conversion of DMU decreased with increased DMU concentration and a maximum of ~82% of both MMC yield and DMU conversion were obtained when a

lower DMU concentration was employed (0.4.5 Kmol/m^3). However, selectivity for MMC was not affected with increase in DMU concentration. The decreased yield of MMC was expected due to increased urea concentration as the ratio of urea to catalyst increased (at constant catalyst concentration). Hence, under such conditions yields and conversions were expected to decrease for a fix reaction time and was not due to deactivation of catalyst.

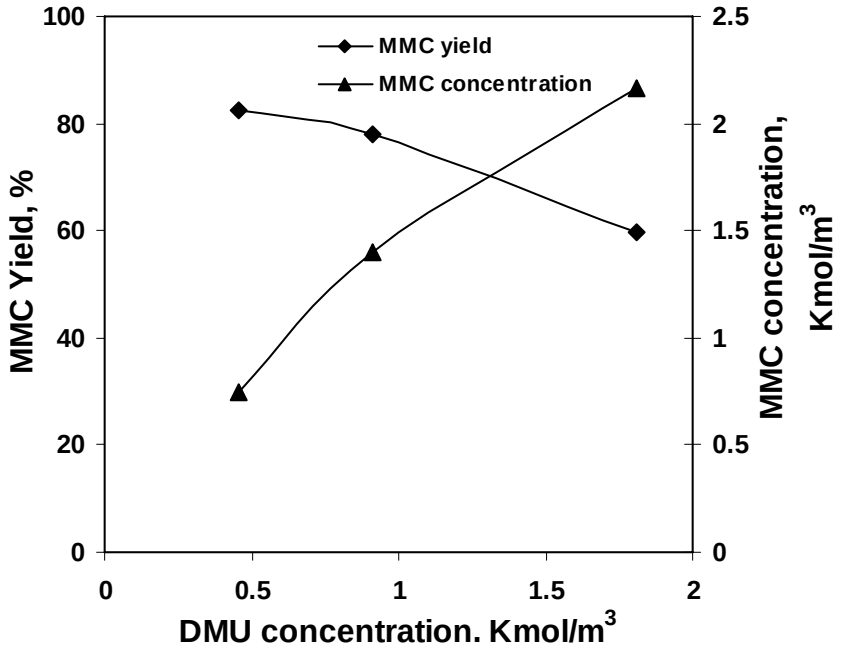


Fig. 2.5. Effect of DMU concentration on MMC yield

Reaction conditions: DBTO, 1.81mmol; DMC, 55.56 mmol; T, 423 K; Time, 4 h; N_2 pressure, 3.4 MPa; Agitation speed, 16.7 Hz; Solvent, Toluene; Total volume, 17 ml.

2.3.1.3.4. Effect of DMC concentration on MMC synthesis

The effect of DMC concentration on MMC yield was investigated in concentration range of 1.65-9.92 Kmol/m^3, reactions were carried out at constant DMU concentration the results are presented in Figure 2.6. The yield of MMC increased

sharply as DMC concentration was increased and in extreme case when pure DMC was employed as reactant maximum yield of 91% of MMC was obtained.

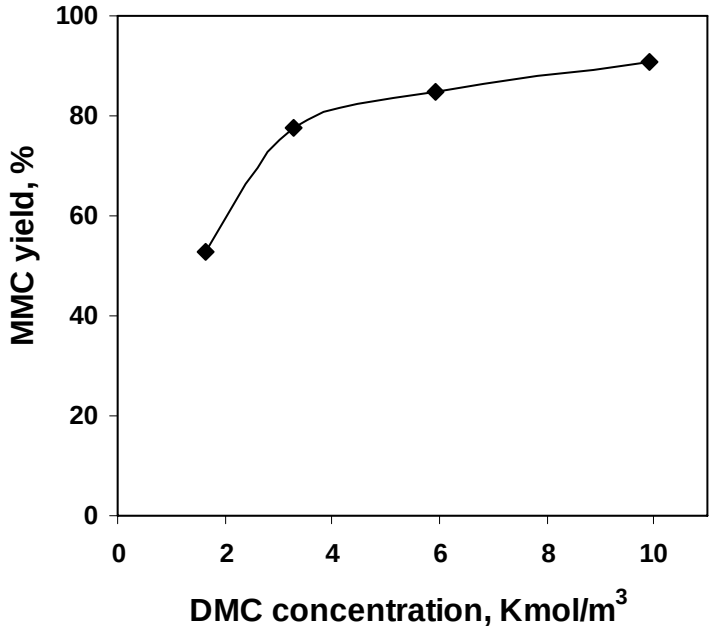


Fig. 2.6. Effect of DMC concentration on MMC yield

Reaction conditions: DBTO, 1.81mmol; DMU, 15.34 mmol; T, 423 K; Time, 4 h; P_{N2}, 3.4 MPa; Agitation speed, 16.7 Hz; Solvent, Toluene; Total volume, 17 ml.

2.3.1.3.5. Effect of solvent on MMC synthesis

The effect of various solvents such as *o*-dichlorobenzene (ODCB), toluene, dimethyl formamide (DMF), diphenyl ether (DPE) and DMC was investigated and the results are presented in Figure 2.7. It can be seen from this figure that polar solvents such as DMF, DMC and ODCB have no significant advantage over non-polar solvent like toluene. The highest yield obtained was with DMC as a solvent and it was due to a synergic effect of DMC acting as a reactant as well as solvent.

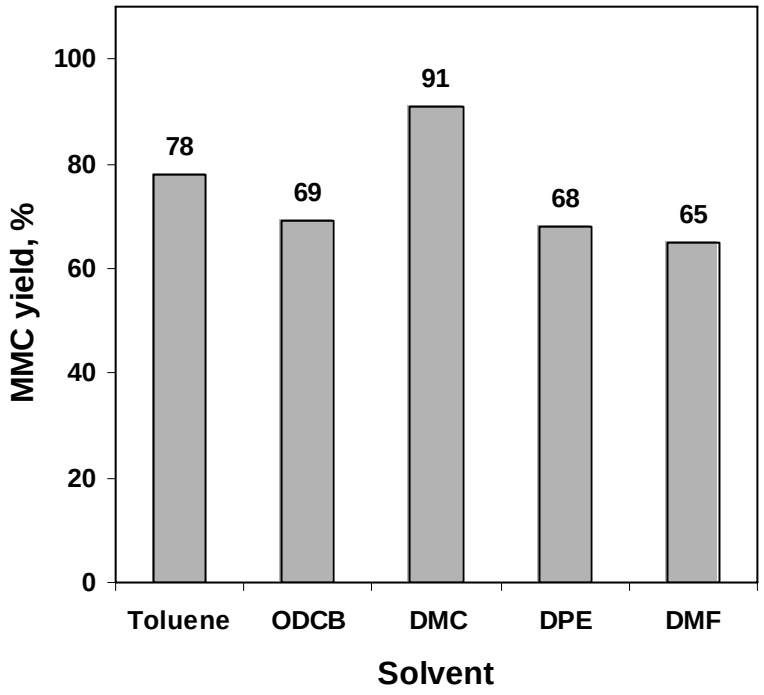


Fig. 2.7. Effect of solvent on MMC yield

Reaction conditions: DBTO, 1.81mmol; DMU, 15.34 mmol; T, 423 K; Time, 4 h; N_2 pressure, 3.4 MPa; Agitation speed, 16.7 Hz; Solvent, Toluene; Total volume, 17 ml.

2.3.1.3.6. Effect of temperature on MMC synthesis

The effect of temperature on MMC formation rate was investigated in the range 413- 433 K. For this purpose catalyst DBTO was pretreated at 423 K with DMC under 3.4 MPa of N_2 for 1 h in a pressure reactor and a fix amount of this pretreated catalyst solution (stored under N_2) was later used for temperature effect study. The pretreatment of catalyst avoided the complexities arising from the effect of temperature on induction period and gave more consistent and realistic initial rates for temperature parameter effect. Figure 2.8 shows that MMC yield increases with increase in temperature using DBTO as catalyst. From this figure the apparent activation energy obtained from Arrhenius law was found to be 34.3 KJ/mol. The low value of activation energy reflected

the secondary role played by catalyst DBTO, which was expected for the reaction as in absence of catalyst appreciable yields of MMC was obtained (Section 2.3.1.3.1. on effectiveness of DBTO catalyst).

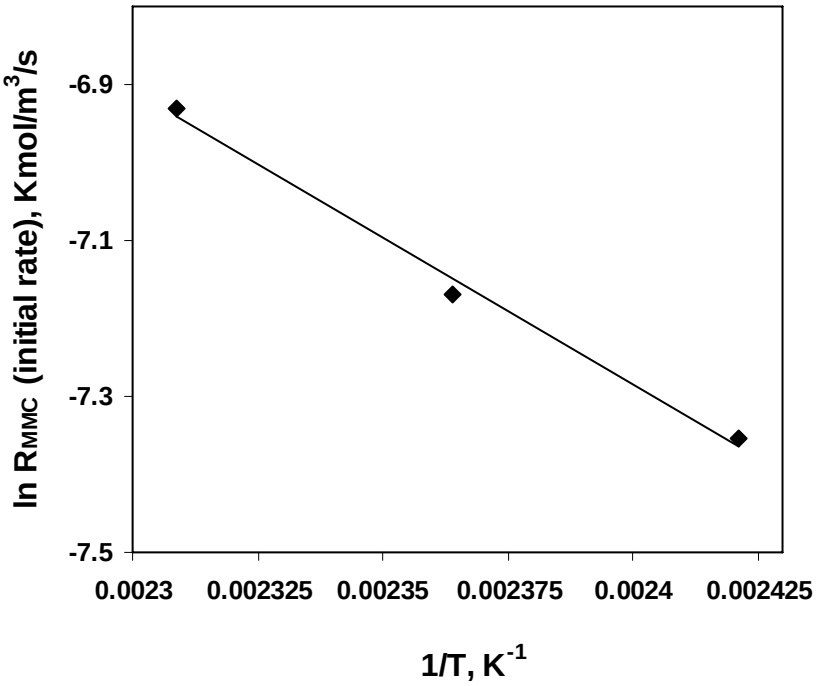


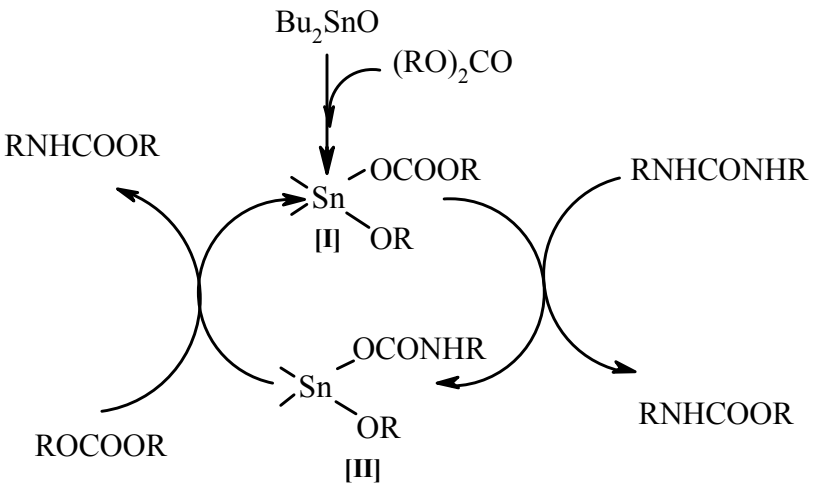
Fig. 2.8. Temperature dependence of initial rate of MMC

Reaction conditions: DBTO, 1.81mmol; DMU, 15.34 mmol; DMC, 169.2 mmol; T, 423 K; Time, 0.5 h; N_2 pressure, 3.4 MPa; Agitation speed, 16.7 Hz; Total volume, 17 ml.

2.3.1.4. Plausible reaction mechanism

Basic tin complex such as DBTO is known to interact with organic carbonate[14] indicating that interaction of carbonate with DBTO is more likely to be the first step towards activation of substrates in our case. Sucia et al.[23] have proposed the dialkyl tin compounds (e.g. DBTO) catalyzed mechanism for the synthesis of dialkyl carbonate from alkyl carbamates and alcohol. Based on their study, a plausible pathway for the formation of *N*-substituted carbamates from substituted ureas and carbonates is depicted

in Scheme 2.4. The basic DBTO was believed to play a key role as a nucleophile attacking carbonyl carbon of carbonate forming catalytically active species, dibutyl alkoxy carbonato tin [**I**].[12b] Species [**I**] interacted with substituted urea to eliminate one molecule of carbamate forming dibutyl alkoxy carbamato tin species [**II**].[22] A further reaction of species [**II**] with carbonate resulted in the formation of one more molecule of carbamate with regeneration of active species [**I**]. The key step here was the formation of species [**I**], which presumably does not get converted into $Bu_2Sn(OR)_2$ because of the presence of urea. However, further work in this area is necessary to arrive at a definitive mechanism for carbamate formation from substituted urea and carbonate catalyzed by tin complexes.



Scheme 2.4: DBTO catalyzed proposed mechnism for carbamate synthesis from urea and carbonate

2.3.2. CARBAMATE SYNTHESIS USING HETEROGENEOUS CATALYST

Though homogeneous catalyst DBTO is highly active for carbamate synthesis from substituted urea and carbonate, the main drawback of this homogeneous catalyst is the separation of catalyst from the product. Hence, various heterogeneous acid/base catalysts were employed for the carbamate synthesis (Table 2.6). Catalyst screening was carried out for the reaction of *N,N'*- diphenyl urea and diphenyl carbonate to phenyl *N*-phenyl carbamate as model. From the catalyst screening it was observed that basic catalyst showed excellent activity over acidic catalyst. Also, from the earlier literature, it is known that basic catalysts are highly efficient for reactions involving carbonate e.g. carboalkoxylation, *trans*- esterification and alkylation. Acidic Al_2O_3 was found inactive for carbamate synthesis (Table 2.6, entry 3) while solid-base catalysts like, $PbZrO_3$, Mg-Al Htlc and Li-MgO were found to give excellent yields of carbamates (90-95% yield, entry 5-7). From the catalyst screening, it was also found that silica gel (W.R. Grace) was highly efficient catalyst for carbamate synthesis and its catalytic activity could be attributed to the interactions of organic carbonate and urea with silanol groups.[23] The variation in activity of silica gel catalysts procured from two different sources viz. W.R Grace and Davisil (entry1 and 2) is thought to be due to the difference in distribution of silanol groups in these two silicas. Na-ZSM-5 catalyst with Si/Al ratio of 130 essentially behaved like SiO_2 since at these high ratio of Si/Al, contribution of Al atom in zeolite framework was very less. The activity in this zeolite is likely to be due to basic sites created by oxygen atom and not by Lewis sites due to Al atom.[24]

Table 2.6. Synthesis of carbamates using solid acid/base catalysts

$R^1NH\,CO\,NHR^1 + R^2OCOOR^2 \longrightarrow 2\ R^1NHCO\,OR^2$

Entry	R^1 (urea)	R^2 (carbonate)	Catalyst	Time, (h)	Yield (%)
1	C_6H_5	C_6H_5	Silica gel[a]	3	81
				8	96
2	C_6H_5	C_6H_5	Silica gel[b]	3	23
3	C_6H_5	C_6H_5	Al_2O_3 (acidic)	3	0
4	C_6H_5	C_6H_5	5% Pb on Silica gel[a]	3	18
5	C_6H_5	C_6H_5	$PbZrO_3$	3	92
6	C_6H_5	C_6H_5	Mg-Al Htlc	3	95
7	C_6H_5	C_6H_5	Li-MgO[c]	3	90
8	C_6H_5	C_6H_5	Na-ZSM-5 (Si/Al=130)	3	79
9	2-Cl-C_6H_4	C_6H_5	Silica gel[a]	8	73[a]
10	3-Cl-C_6H_4	C_6H_5	Silica gel[a]	8	79
[11]	4-Cl-C_6H_4	C_6H_5	Silica gel[a]	8	89
12	3-$NO_2C_6H_4$	C_6H_5	Silica gel[a]	8	89
13	4-CH_3-C_6H_5	C_6H_5	Silica gel[a]	8	91
14[d]	C_6H_5	CH_3	Silica gel[a]	8	18
15[d]	C_6H_5	C_2H_5	Silica gel[a]	8	10
16[d]	CH_3	CH_3	Silica gel[a]	8	81

Reaction conditions: substituted urea, 3.16 mmol; carbonate, 15.6 mmol; catalyst,0.2 g; T, 423 K; Agitation speed, 16.7 Hz; N_2 atmosphere; [a] Silica gel from W.R. Grace, USA ; [b] Silica gel davisil, Aldrich, USA reaction T, 373 K; [c] Prepared by wet impregnation of LiOAc on $Mg(OAc)_2$ followed by calcination at 993 K (Li/Mg = 0.1); [d] reactions were carried out in a 50 ml autoclave using 17ml of carbonate and under N_2 pressure of 3.4 MPa.

The most intriguing aspect of heterogeneous catalyst is catalyst recycle. Hence, the reusability of silica gel and Na-ZSM-5 catalyst was studied and the results are shown in Figure 2.9. Recycling of catalyst was carried out by filtration of catalyst from crude reaction mixture in acetone followed by drying of catalyst and calcination at 773 K for 3 h. The catalyst recycle result showed excellent reusability of both catalysts for up to five recycles without any loss in their catalytic activity.

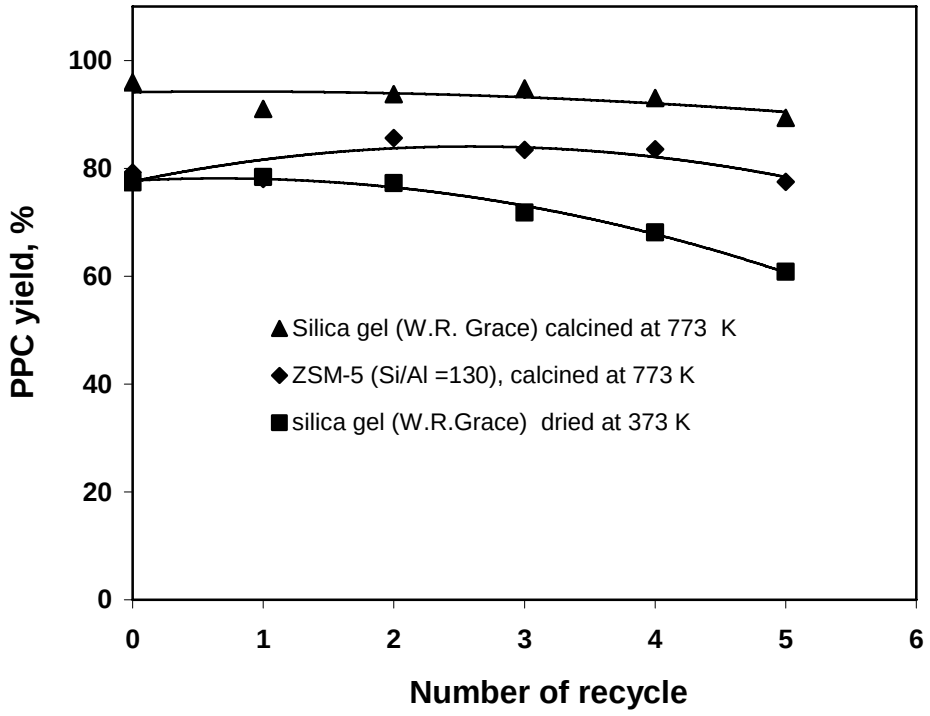


Figure 2.9. Catalyst recycles

Reaction conditions: Catalyst, 0.2 g; DPU, 3.16 mmol; DPC,15.4 mmol; T, 423 K; Time, 8 h; N2 atmosphere; Agitation speed, 16.7 Hz; Total volume, 4 x 10^{-6} m^3.

2.4. CONCLUSION

An environmentally benign route for the synthesis of carbamates via transfunctionalization of substituted ureas and organic carbonates using homogeneous as well as heterogeneous catalysts was demonstrated for the first time. This methodology is simple and highly efficient for carbamate synthesis, and shows 100% atom economy. High yield of carbamates were obtained by using homogeneous dibutyl tin oxide (DBTO) as well as heterogeneous silica gel catalyst, which was easily recycled. It was observed that there was no loss in catalytic activity of silica gel even after five recycles. Reactivity study of substituted ureas and organic carbonate was investigated and it was observed that aliphatic ureas showed higher reactivity compared to aromatic ureas due to their basicity. Various electron donating or electron withdrawing substituents (e.g. CH_3, Cl and NO_2) on aromatic urea did not show any significant effect on urea reactivity compared to non-substituted aromatic urea i.e. diphenyl urea. The reactivity of alkyl carbonates towards ureas was found to decrease in the order, dimethyl carbonate> diethyl carbonate > dibutyl carbonate as steric hindrance increased from dimethyl carbonate to dibutyl carbonate. Reaction parameter effects on the synthesis of industrially important methyl *N*-methyl carbamate were investigated. The Arrhenius activation energy for the reaction between *N*,*N*'-dimethyl urea and dimethyl carbonate was found to be 34.3 KJ/mol. A reaction mechanism has been also postulated explaining the role of DBTO in the synthesis of carbamate from urea and carbonates.

2.5. IDENTIFICATION OF CARBAMATES

Carbamates were isolated in pure form and fully characterized by elemental analysis, ^{1}H NMR, ^{13}CNMR, IR and GC-MS.

Phenyl *N*-Phenyl carbamate (1a): IR (KBr) υ_{CO}: 1717 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.95δ (s, 1H, NH), 7.46-7.09 (m, 10H, Ar-CH);. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 118.84 (Ar-C), 121.61(Ar-C), 123.90 (Ar-C), 125.66 (Ar-C), 129.11 (Ar-C), 129.37 (Ar-C), 137.38 (Ar-C-N), 150.6 (C=O), 151.64(Ar-C-O). GC/MS (EI, 70 eV): **1a** thermally decomposes to Phenyl isocyanate and Phenol, therefore; it was indirectly identified by its decomposition products. Phenyl isocyanate, (m/z): 119, 91, 64, 51 and Phenol, (m/z): 94, 66, 39. Microanalysis for $C_{13}H_{11}NO_2$, Calculated: 73.23% C, 5.16% H, 6.57% N; found: 72.85% C, 5.27% H, 6.35% N.

Phenyl *N*-(3-Cl-phenyl) carbamate (1c): IR (KBr) υ_{CO}: 1714 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.97 (s, 1H, NH), 7.57-7.07 (m, 9H, Ar-CH);. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 118.96 (Ar-C), 120.85 (Ar-C), 121.52 (Ar-C), 125.8 (Ar-C), 126.27 (Ar-C), 129.54 (Ar-C), 130.01 (Ar-C), 134.77 (Ar-C-Cl), 138.62 (Ar-C-N), 150.43 (C=O), 151.51(Ar-C-O). GC/MS (EI, 70 eV): **1c** decomposes to *N*-(3-Cl-phenyl) isocyanate and Phenol. *N*-(3-Cl-phenyl) isocyanate, (m/z): 153, 125, 90, 63, 50 and Phenol, (m/z): 94,66,39. Microanalysis for $C_{13}H_{10}NO_2Cl$, Calculated: 63.03% C, 4.04% H, 5.65% N, 14.34% Cl; found: 63.4% C, 4.02% H, 5.56% N, 13.97% Cl.

Phenyl *N*-(4-Cl-phenyl) carbamate (1d): IR (KBr) υ_{CO}: 1716 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.98 (brs, 1H, NH), 7.45-7.17 (m, 9H, Ar-CH). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 120.30 (Ar-C), 121.55 (Ar-C), 125.83 (Ar-C), 129.02 (Ar-C), 129.15 (Ar-C), 129.43 (Ar-C-Cl), 135.98 (Ar-C-N), 150.46 (C=O), 151.41 (Ar-C-O). GC/MS (EI, 70 eV): **1d** decomposes to *N*-(4-Cl phenyl) isocyanate and Phenol. *N*-(4-Cl phenyl) isocyanate, (m/z): 153, 125, 90, 63, 50 and Phenol, (m/z): 94, 66, 39. Microanalysis for $C_{13}H_{10}NO_2Cl$, Calculated: 63.03% C, 4.04% H, 5.65% N, 14.34%.

Phenyl *N*-(3-NO_2 –phenyl) carbamate (1e): IR (KBr) υ_{CO}: 1712 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.16 (dd, *J* = 1.6 & 7.5 Hz, 2H, Ar-CH), 7.22 (dd, *J* = 1.6 & 7.5 Hz, 1H, Ar-CH), 7.3 (brs, 1H, NH), 7.37 (dd, *J* = 1.6 & 7.5 Hz, 2H, Ar-CH), 7.45 (t, *J* = 7.95

Hz, 1H, Ar-$CH_{meta\ to\ NO2}$), 7.7 (d, *J* = 7.95 Hz, 1H, Ar-$CH_{para\ to\ NO2}$), 7.92 (dd, *J* = 1.6 & 7.95 Hz, 1H, Ar-$CH_{ortho\ to\ NO2}$), 8.31 (t, *J* = 1.6 Hz, 1H, Ar-$CH_{ortho\ to\ NO2}$), ^{13}C NMR (500 MHz, $CDCl_3$): δ = 113.66 (Ar-C), 118.42 (Ar-C), 121.45 (Ar-C), 124.42 (Ar-C), 126.01 (Ar-C), 129.46 (Ar-C), 129.86 (Ar-C), 138.69 (Ar-C-N), 148.66 (Ar-C-NO_2), 150.22 (C=O), 151.7 (Ar-C-O). GC/MS (EI, 70 eV): **1f** decomposes to *N*-(3-NO_2 phenyl) isocyanate and Phenol. *N*-(3-NO_2 phenyl) isocyanate, (m/z): 164, 118, 90, 63, 50. Phenol, (m/z): 94, 66, 39. Microanalysis for $C_{13}H_{10}N_2O_4$, Calculated: 60.46% C, 3.87% H, 10.85% N; found: 61.45% C, 3.94% H, 10.52% N.

Phenyl *N*-(4-CH_3 phenyl) carbamate (1f): IR (KBr) υ_{CO}: 1719 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.32 (s, 3H, Ar-CH_3), 6.95 (brs, 1H, NH), 7.43-7.11 (m, 9H, Ar-CH). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 20.69 (CH_3), 118.88 (Ar-C), 121.67 (Ar-C), 125.55 (Ar-C), 126.25 (Ar-C), 129.32 (Ar-C), 129.6 (Ar-C), 134.79 (Ar-C-N), 150.68 (C=O), 151.7(Ar-C-O). GC/MS (EI, 70 eV): **1e** decomposes to *N*-(4-CH_3 phenyl) isocyanate and phenol. *N*-(4-CH_3 phenyl) isocyanate, (m/z): 133, 104, 91, 63, 51. Phenol, (m/z): 94, 66, 39. Microanalysis for $C_{14}H_{13}NO_2$, Calculated: 74% C, 5.72% H, 6.16% N; found: 73.75% C, 5.55% H, 6.38% N.

Methyl *N*-phenyl carbamate (2a): IR (KBr) υ_{CO}: 1708 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.77 (s, 3H, O-CH_3), 6.69 (brs, 1H, NH), 7.4-7.02 (m, 5H, Ar-CH). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 52.21 (O-CH_3) , 118.74 (Ar-C), 123.38 (Ar-C), 128.94 (Ar-C), 137.84 (Ar-C-N), 154.11 (C=O). GC/MS: (m/z): 151, 135, 119, 106, 92, 77, 65, 51, 39. Microanalysis for $C_8H_9NO_2$, Calculated: 63.57% C, 5.96% H, 9.27% N; found: 63.05% C, 5.71% H, 8.98% N.

Ethyl *N*-phenyl carbamate (2b): IR (KBr) υ_{CO}: 1703 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32 (t, 3H, *J* = 7.32 Hz, CH_3-C), 4.22 (q, 2H, *J* = 7.32 Hz, O-CH_2-C), 6.66 (brs, 1H, NH) 7.42-7.03 (m, 5H, Ar-CH). ^{13}C NMR (500 MHz, $CDCl_3$,): δ = 14.45 (CH_3-C), 61.1 (O-CH_2), 118.71 (Ar-C), 123.25 (Ar-C), 128.91 (Ar-C), 137.99 (Ar-C-N), 153.7 (C=O). GC/MS: (m/z): 165, 137, 119, 93, 77, 65, 51, 39. Microanalysis for $C_8H_9NO_2$, Calculated: 65.45% C, 6.66% H, 8.48% N; found: 65.69% C, 6.73% H, 8.46% N.

Butyl *N*-phenyl carbamate (2c): IR (KBr) υ_{CO}: 1702 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97 (t, 3H, *J* = 7.33Hz, CH_3-C), 1.45 (m, 2H, *J* = 6.84Hz & 7.33 Hz, -CH_2-), 1.69

(qu, 2H, *J* =6.35Hz & 6.83Hz, -CH_2-), 4.19 (t, 2H, *J* = 6.35Hz, -CH_2-O), 6.67 (brs, 1H, NH), 7.42-7.04 (m, 5H, Ar-CH);. ^{13}C NMR (500 MHz, $CDCl_3$,): δ = 13.66 (CH_3-C), 19.03 (CH_2-C), 30.95 (CH_2-C), 65.08(O-CH_2), 118.67 (Ar-C), 123.28 (Ar-C), 128.97 (Ar-C), 138.01 (Ar-C-N), 153.76 (C=O). GC/MS: (m/z): 193, 137, 119, 93, 77, 65, 41. Microanalysis for $C_{11}H_{15}NO_2$, Calculated: 68.39% C, 7.77% H, 7.72% N; found: 67.85 % C, 7.78% H, 7.35% N.

Methyl *N*-methyl carbamate (3a): IR (KBr) υ_{CO}: 1711 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.78 (d, 3H, *J* = 4.88 Hz, N-CH_3), 4.93 (brs, 1H, NH); 3.67 (s, 3H, O-CH_3). ^{13}C NMR (500 MHz, $CDCl_3$,): δ = 27.36 (N-CH_3), 51.91 (O-CH_3), 157.77 (C=O). GC/MS (EI, 70 eV), (m/z): 89, 74, 58, 44.

Ethyl *N*-methyl carbamate (3b): IR (KBr) υ_{CO}: 1704 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.16 (t, 3H, *J* = 7.32 Hz, CH_3-C), 2.7 (d, 3H, N-CH_3), 4.018 (q, 2H, *J* = 7.32 Hz, O-CH_2), 4.95 (brs, 1H, NH). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 14.42 (CH_3), 27.17 (N-CH_3), 60.47 (O-CH_2), 157.33 (C=O). GC/MS (EI, 70 eV), (m/z): 103, 88, 74, 58, 44.

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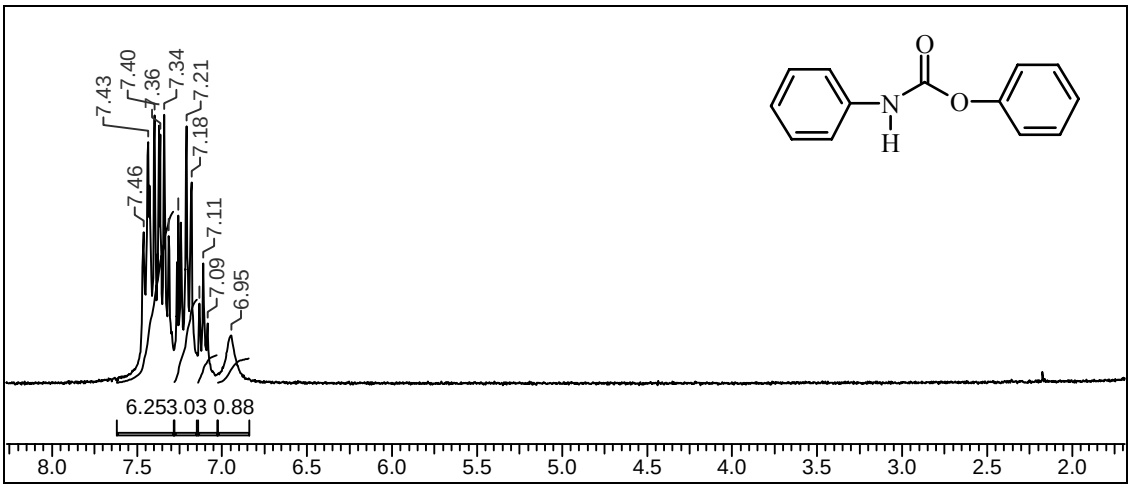
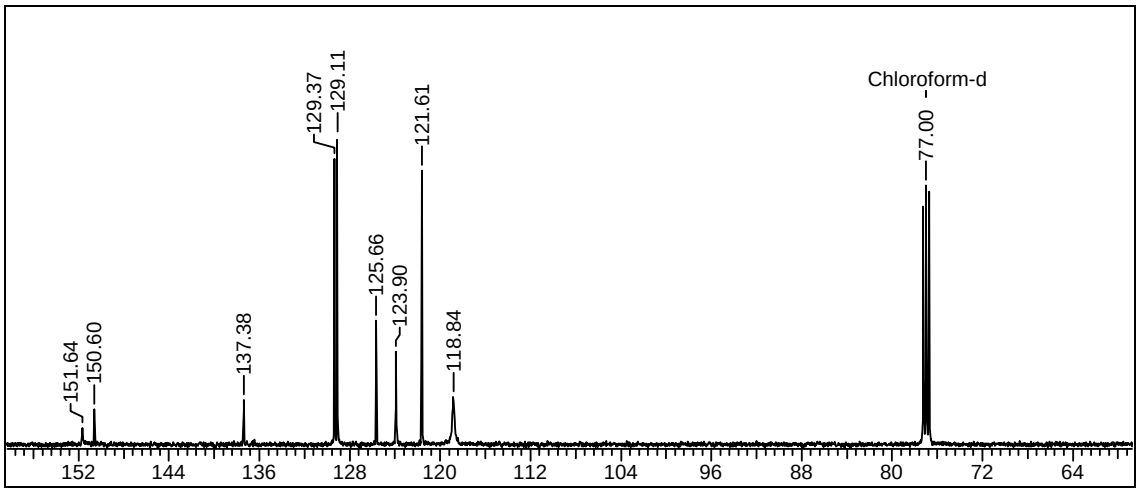
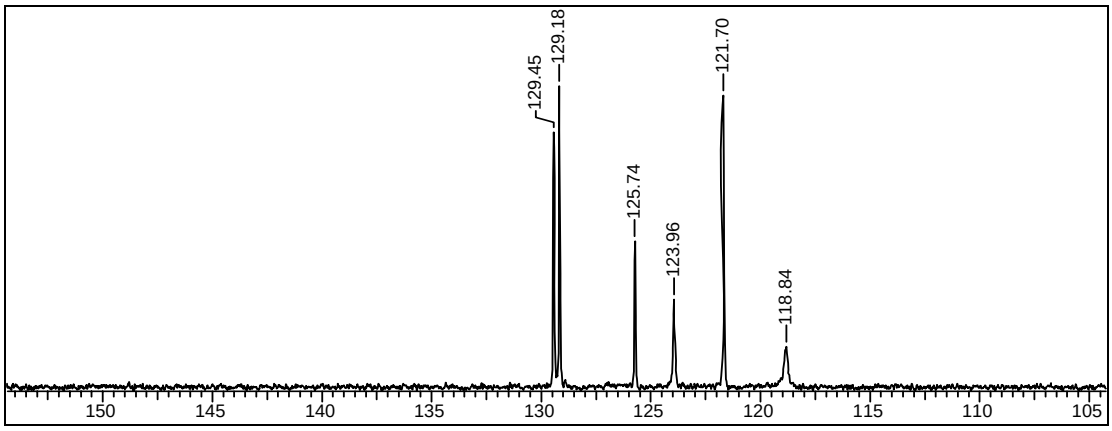
SPECTRA



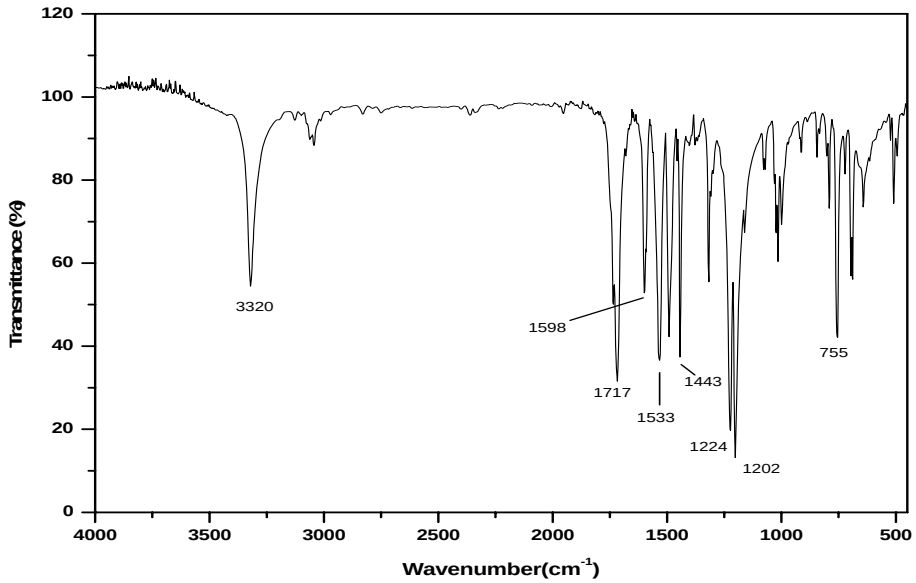
^{1}H NMR Spectrum of compound **1a** ($CDCl_3$, 200 MHz)



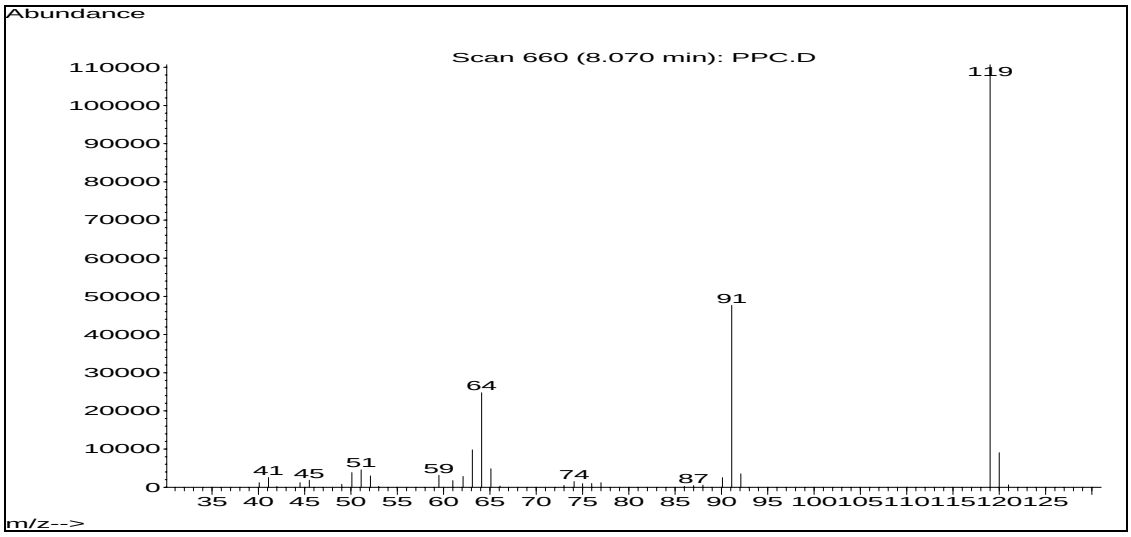
^{13}C NMR Spectrum of compound **1a** ($CDCl_3$, 500 MHz)



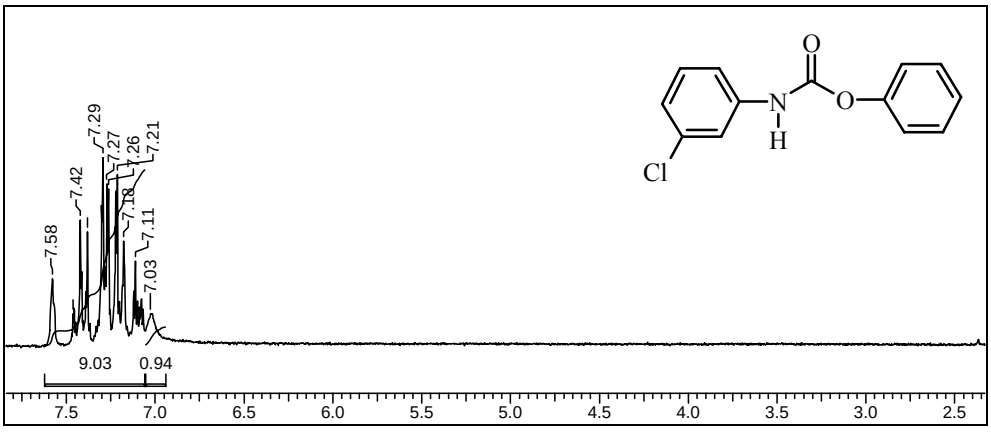
DEPT Spectrum of compound **1a** ($CDCl_3$, 500 MHz)



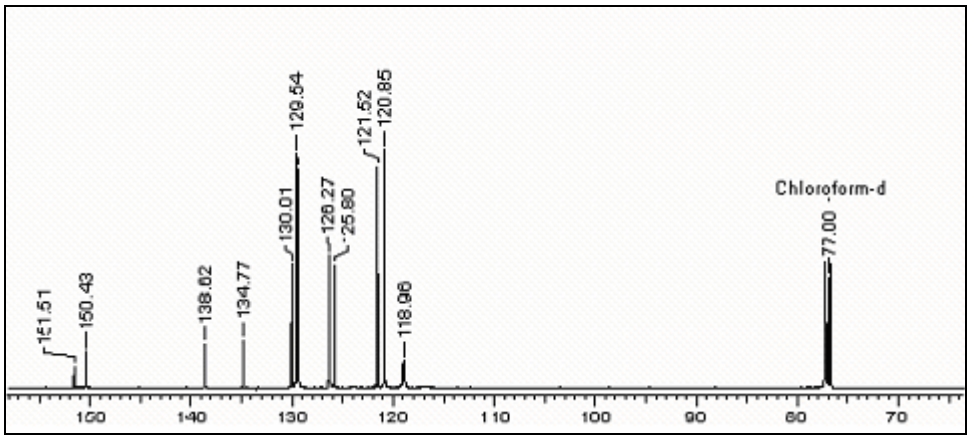
IR Spectrum of compound **1a** (KBr)



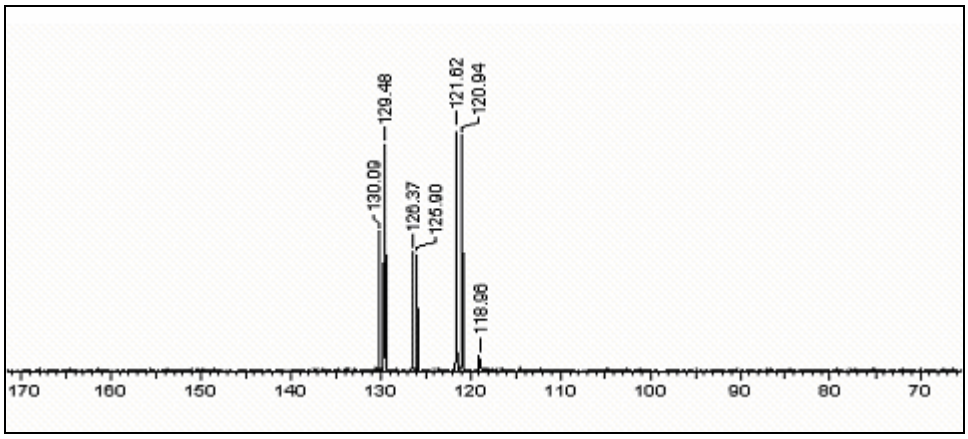
GC-MS Spectrum of **Phenyl isocyanate** (70 eV, EI)



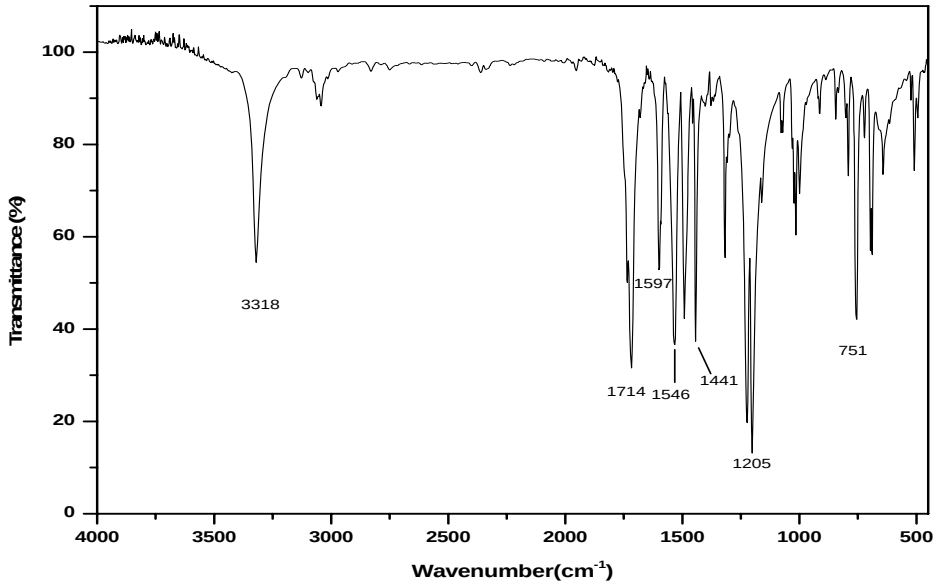
^{1}H NMR Spectrum of compound **1c** ($CDCl_3$, 200 MHz)



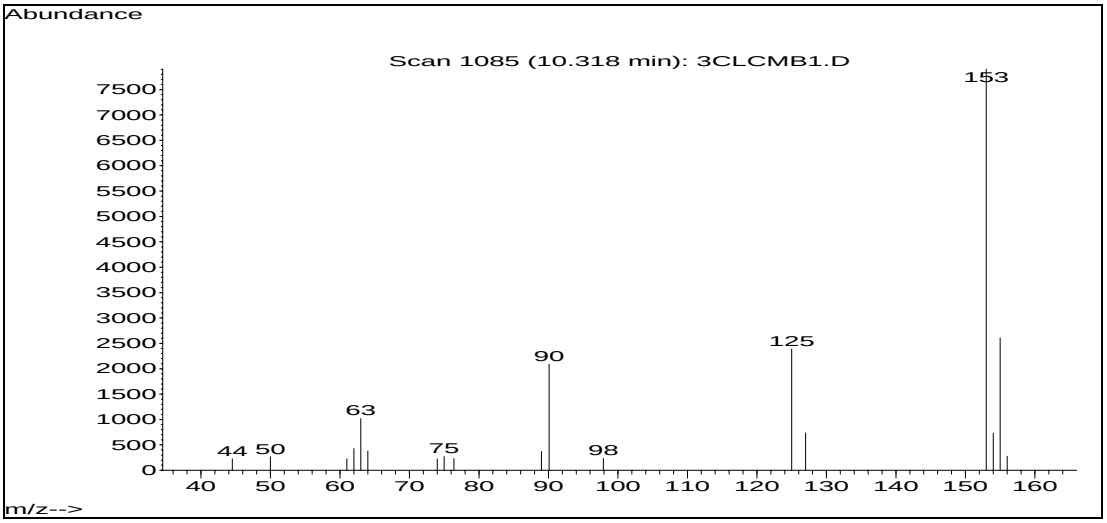
^{13}C NMR Spectrum of compound **1c** ($CDCl_3$, 500 MHz)



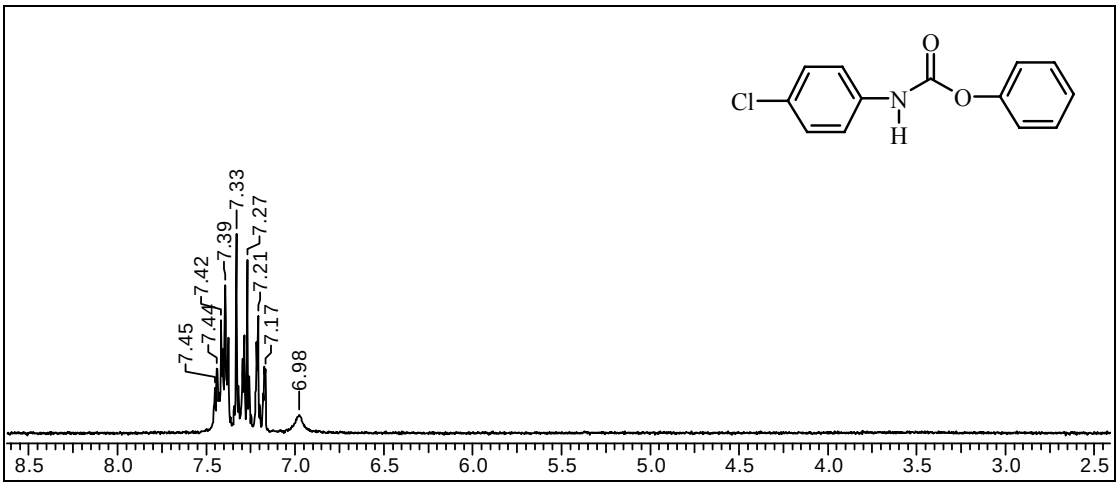
DEPT Spectrum of compound **1c** ($CDCl_3$, 500 MHz)



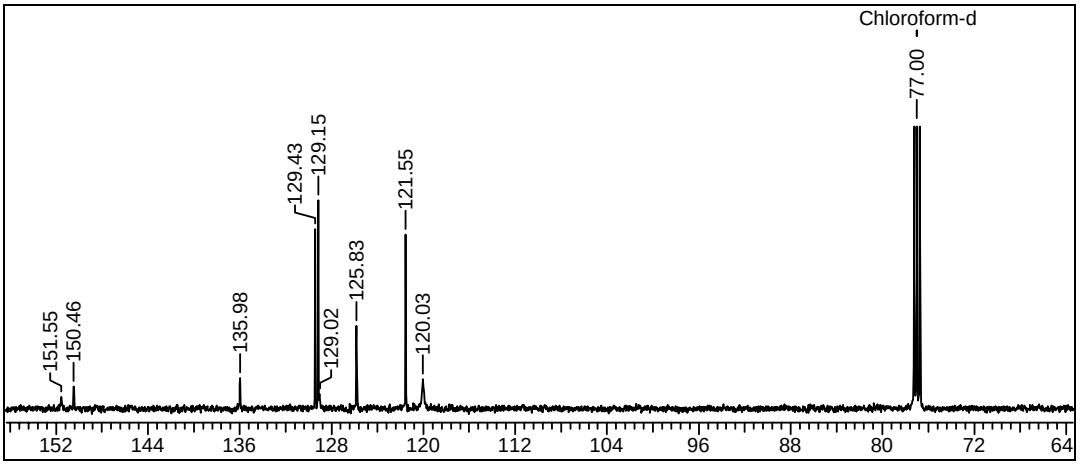
IR Spectrum of compound **1c** (KBr)



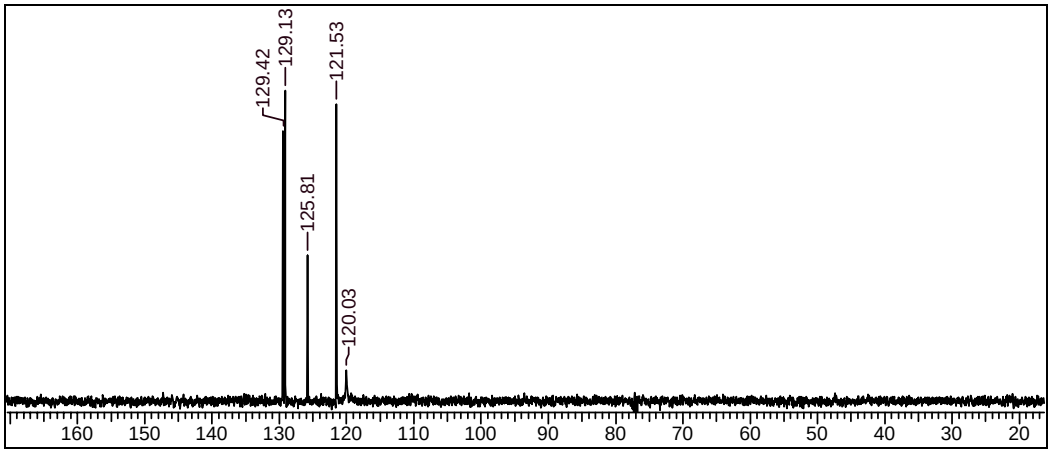
GC-MS Spectrum of ***N*-(3-Cl phenyl) isocyanate** (70 eV, EI)



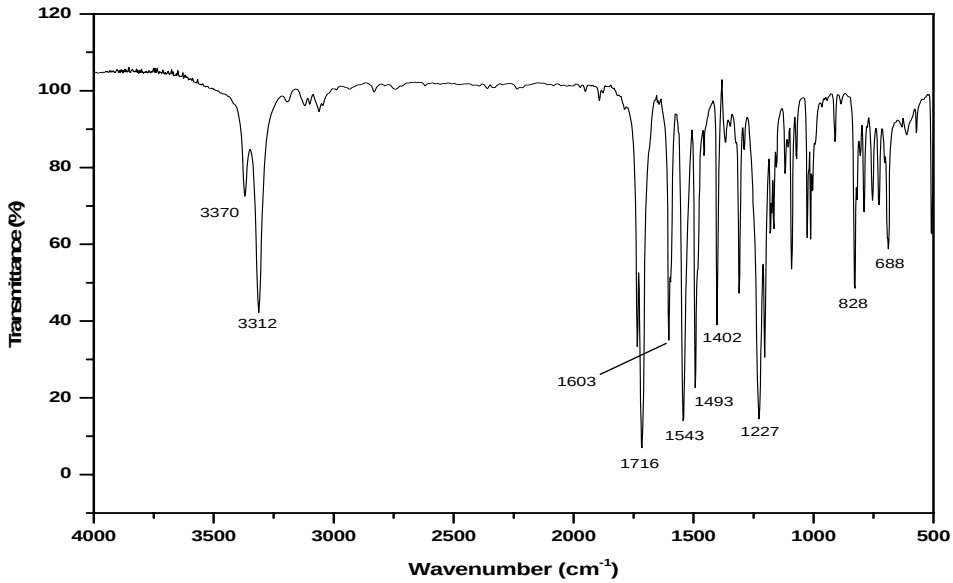
^{1}H NMR Spectrum of compound **1d** ($CDCl_3$, 200 MHz)



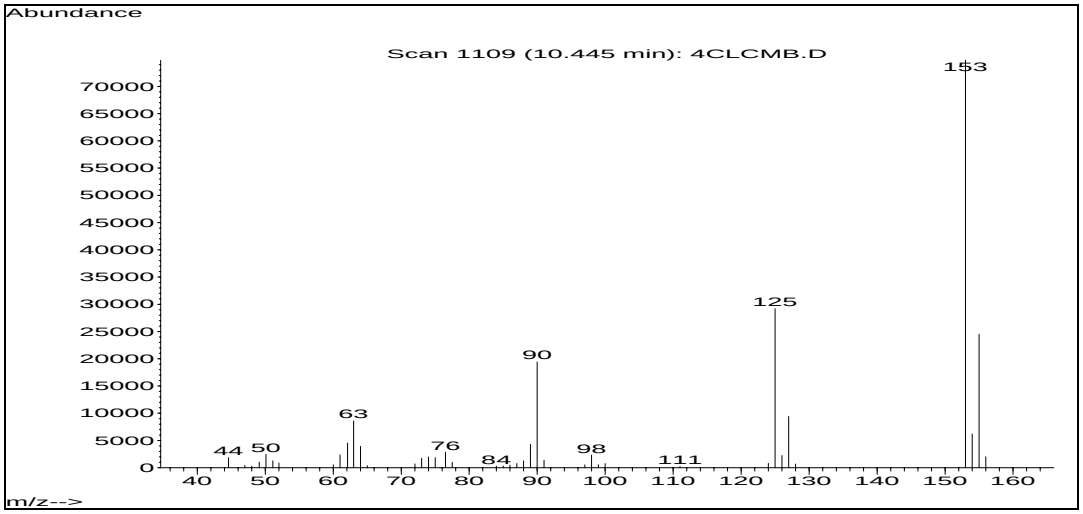
^{13}C NMR Spectrum of compound **1d** ($CDCl_3$, 500 MHz)



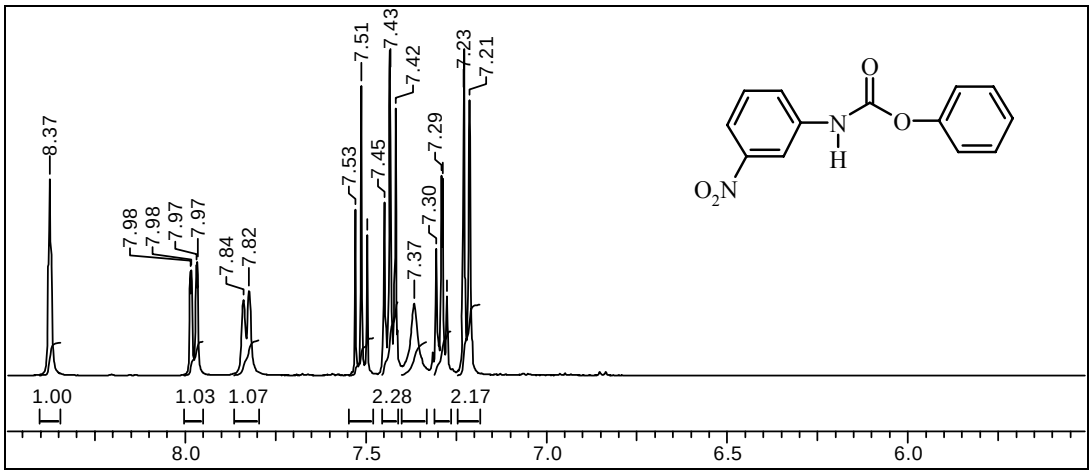
DEPT Spectrum of compound **1d** ($CDCl_3$, 500 MHz)



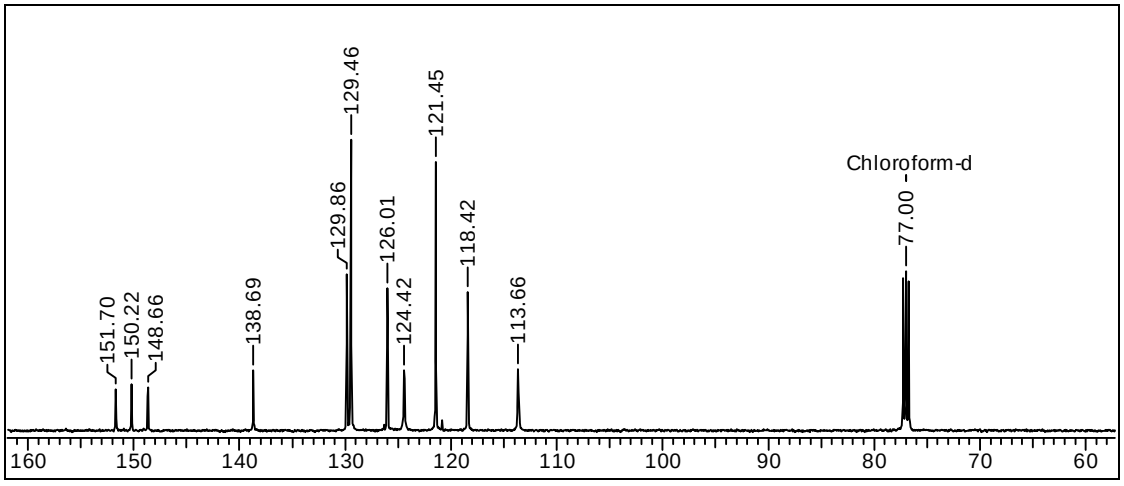
IR Spectrum of compound **1d** (KBr)



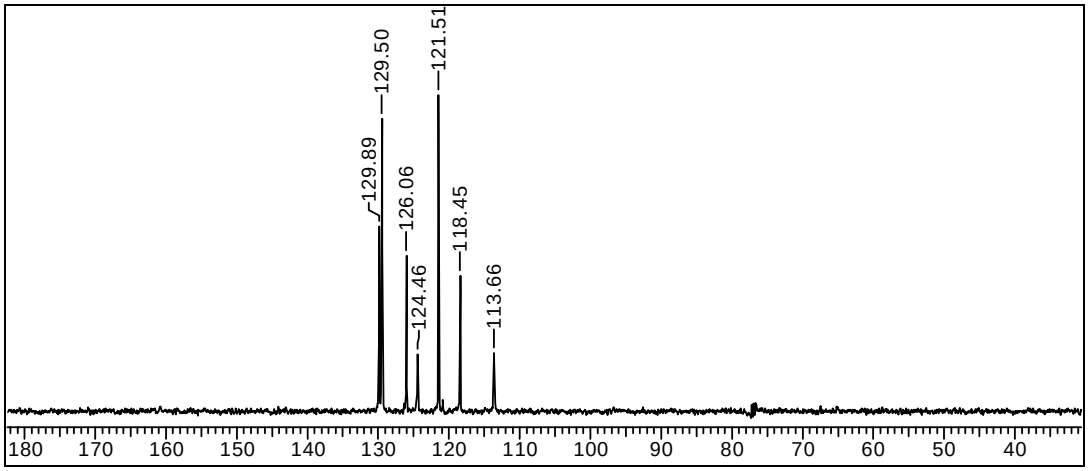
GC-MS Spectrum of ***N*-(4-Cl phenyl) isocyanate** (70 eV, EI)



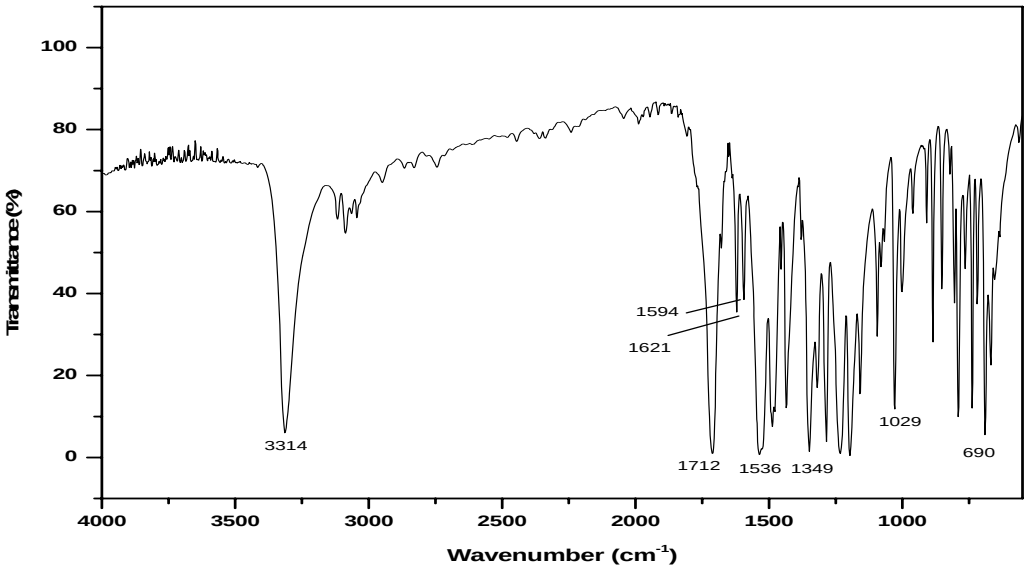
^{1}H NMR Spectrum of compound **1e** ($CDCl_3$, 200 MHz)



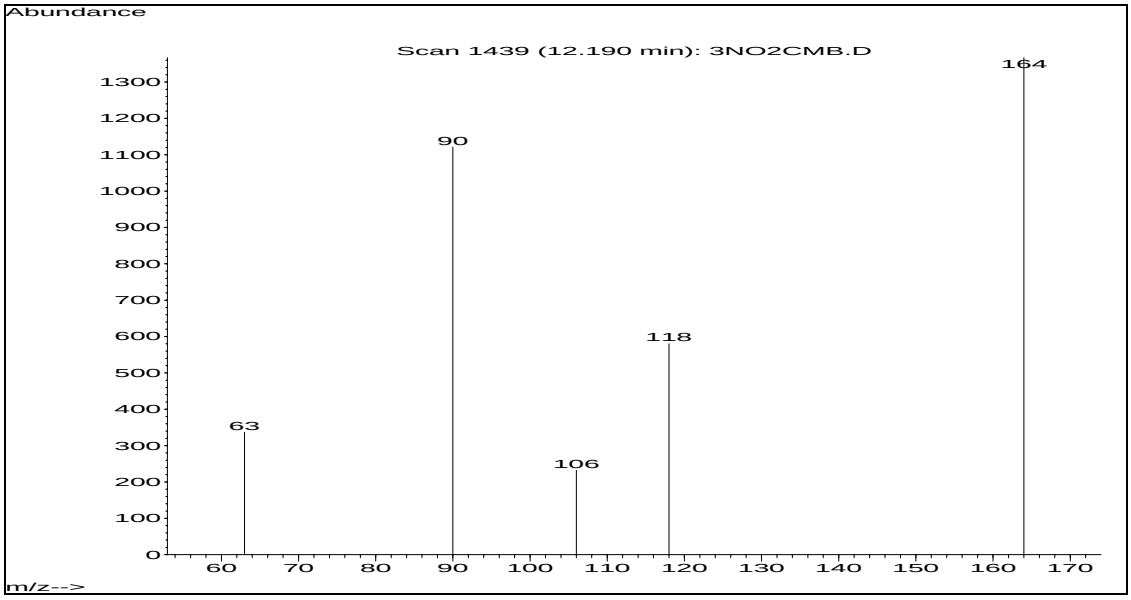
^{13}C NMR Spectrum of compound **1e** ($CDCl_3$, 500 MHz)



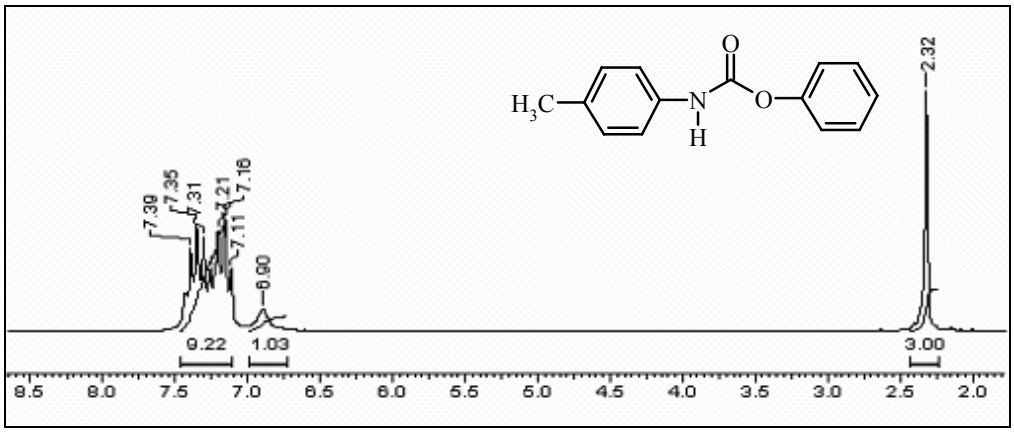
DEPT Spectrum of compound **1e**($CDCl_3$, 500 MHz)



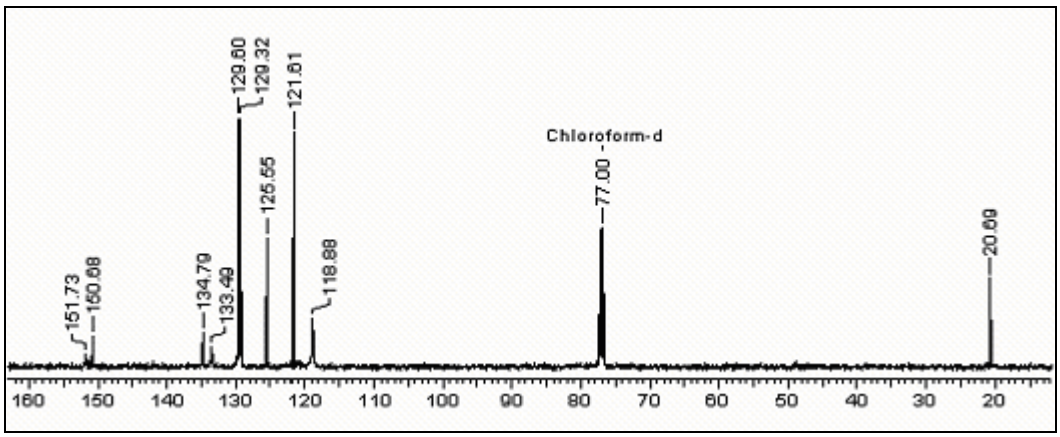
IR Spectrum of compound **1e** (KBr)



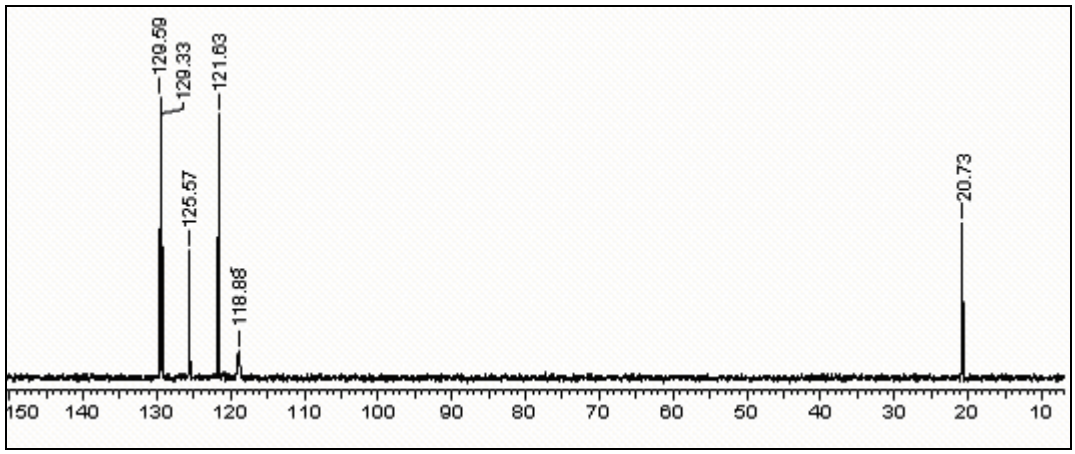
GC-MS Spectrum of ***N*-(3-NO_2 phenyl) isocyanate** (70 eV, EI)



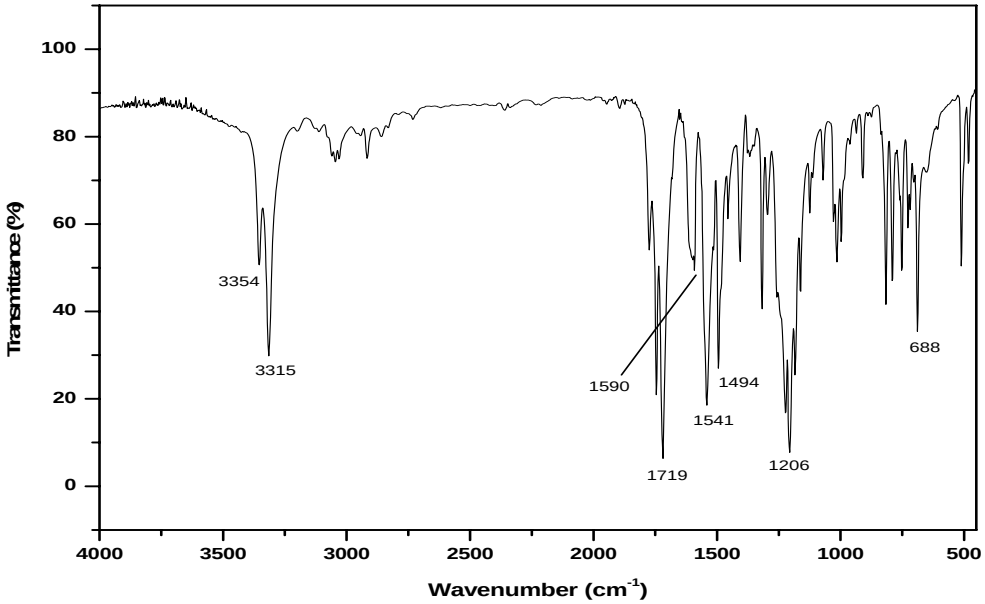
^{1}H NMR Spectrum of compound **1f** ($CDCl_3$, 200 MHz)



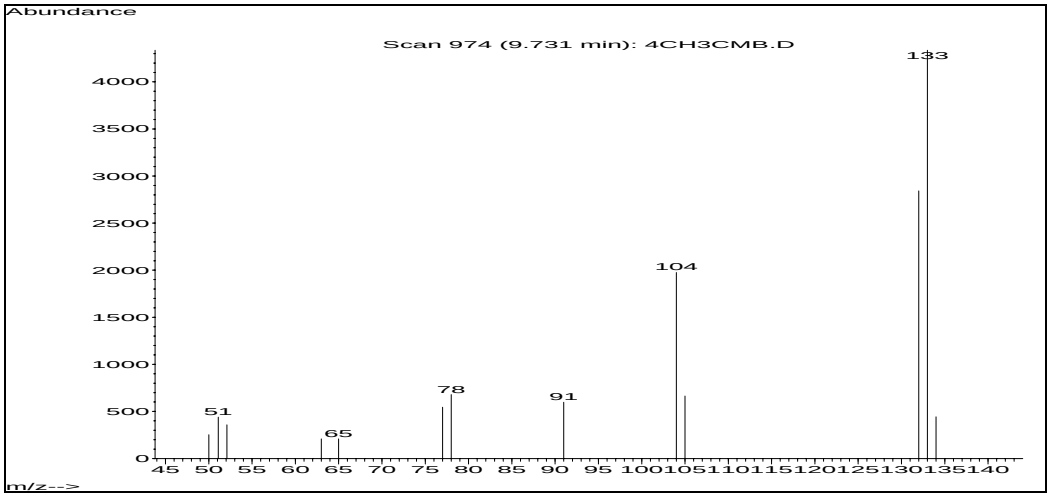
^{13}C NMR Spectrum of compound **1f** ($CDCl_3$, 500 MHz)



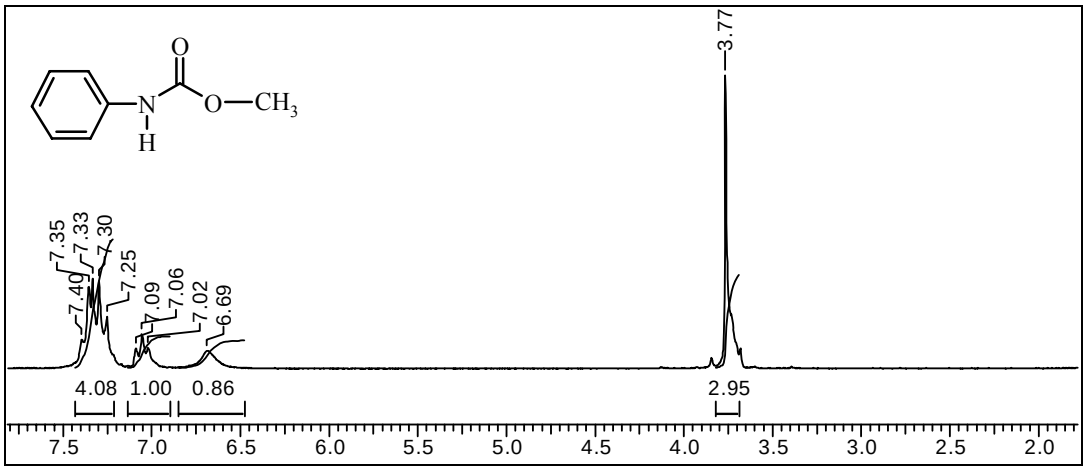
DEPT Spectrum of compound **1f** ($CDCl_3$, 500 MHz)



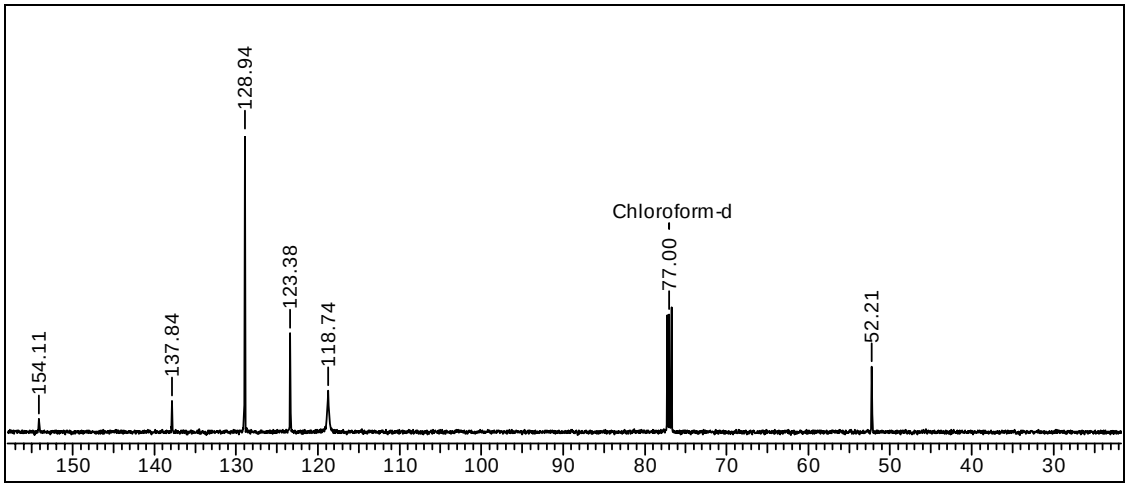
IR Spectrum of compound **1f** (KBr)



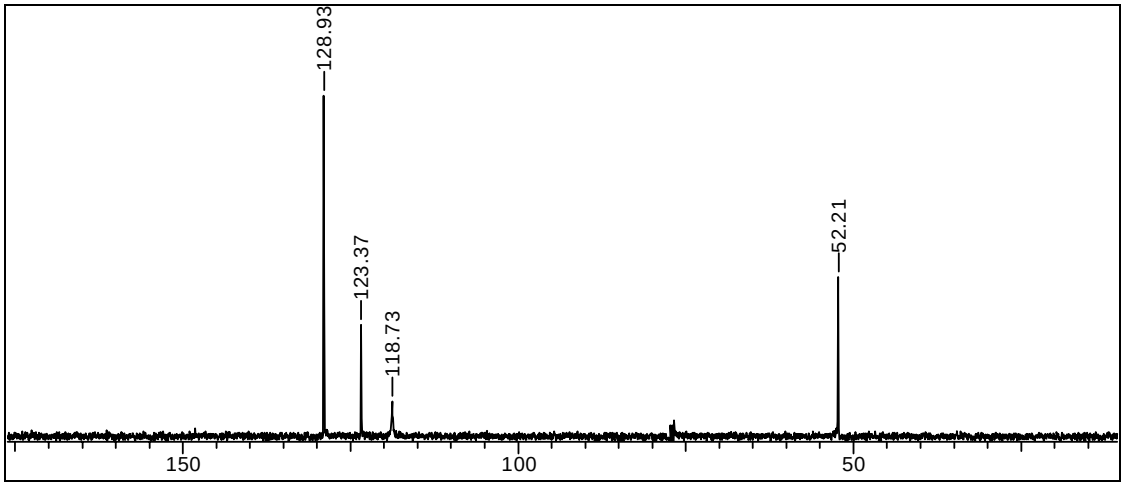
GC-MS Spectrum of ***N*-(4-CH_3 phenyl) isocyanate** (70 eV, EI)



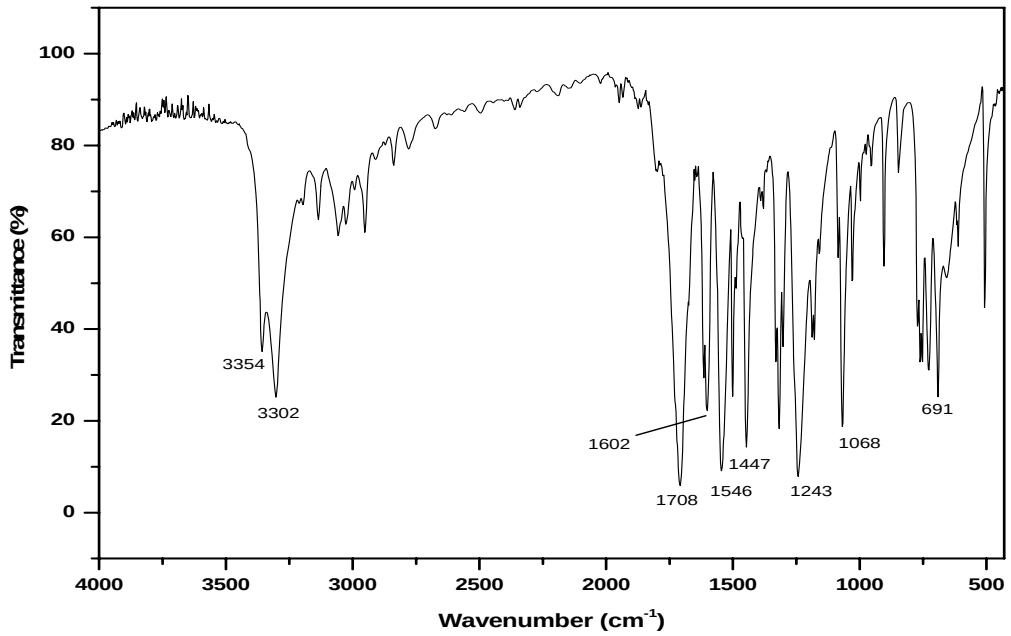
^{1}H NMR Spectrum of compound **2a** ($CDCl_3$, 200 MHz)



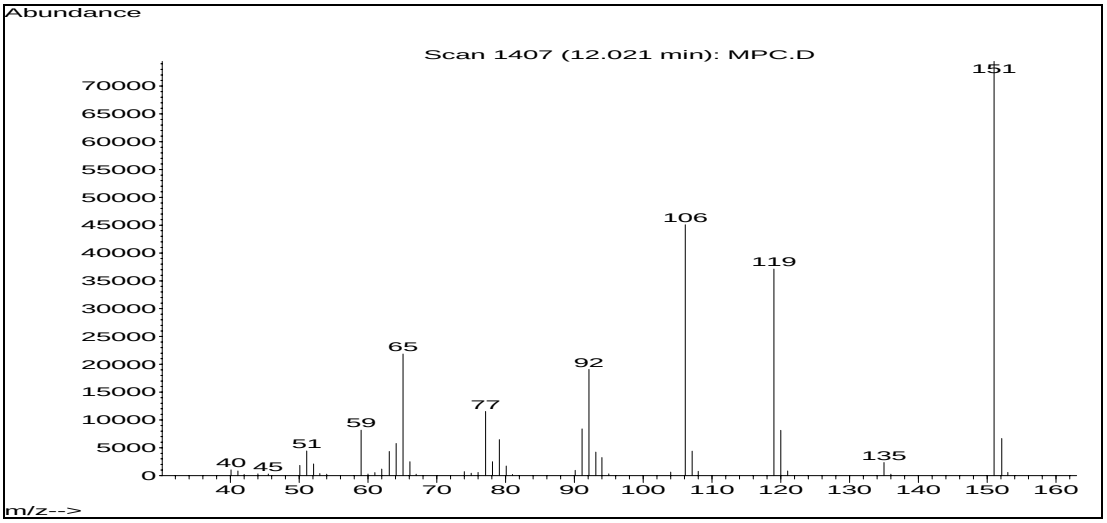
^{13}C NMR Spectrum of compound **2a** ($CDCl_3$, 500 MHz)



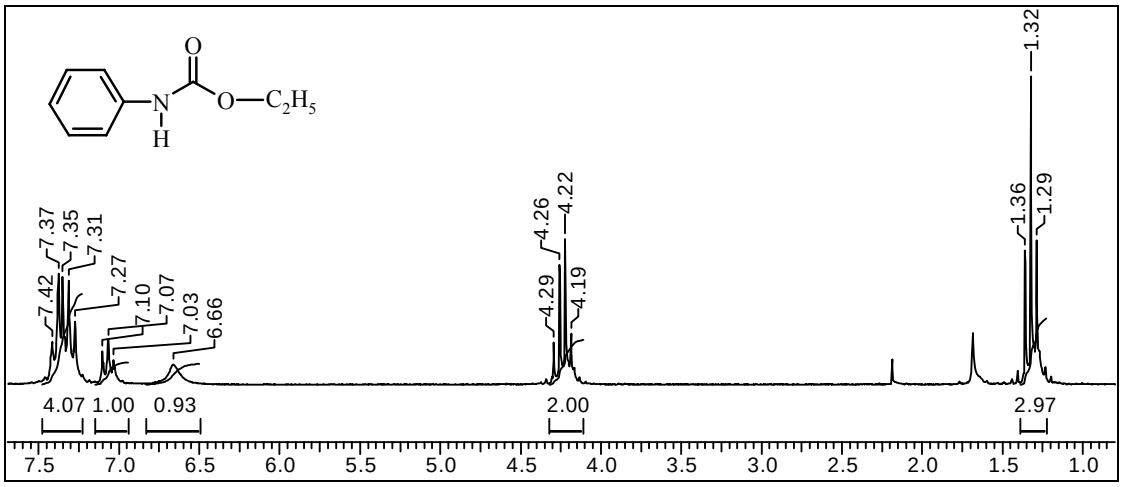
DEPT Spectrum of compound **2a** ($CDCl_3$, 500 MHz)



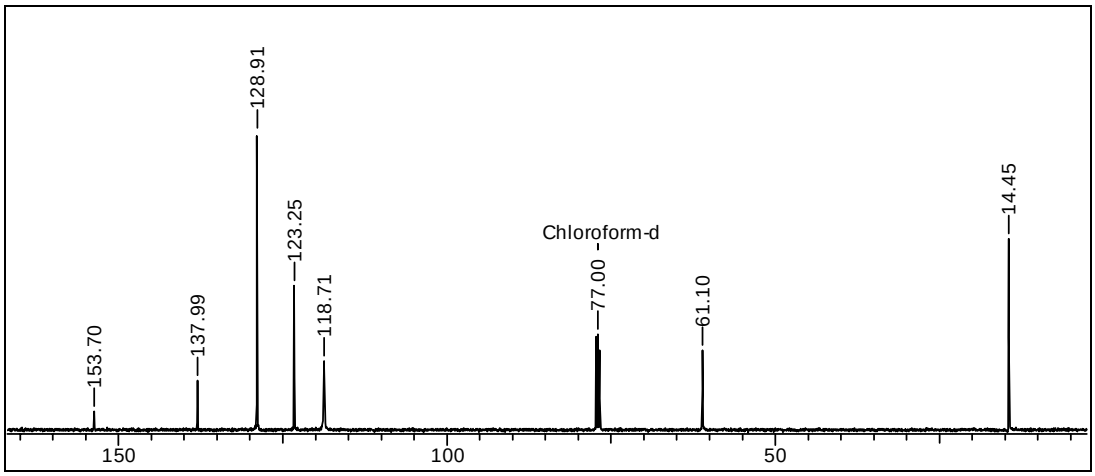
IR Spectrum of compound **2a** (KBr)



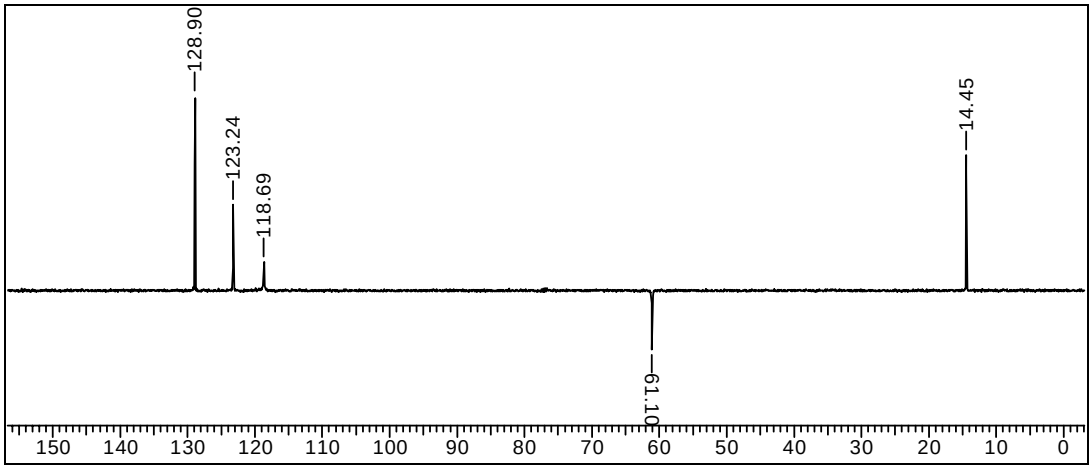
GC-MS Spectrum of compound **2a** (70 eV, EI)



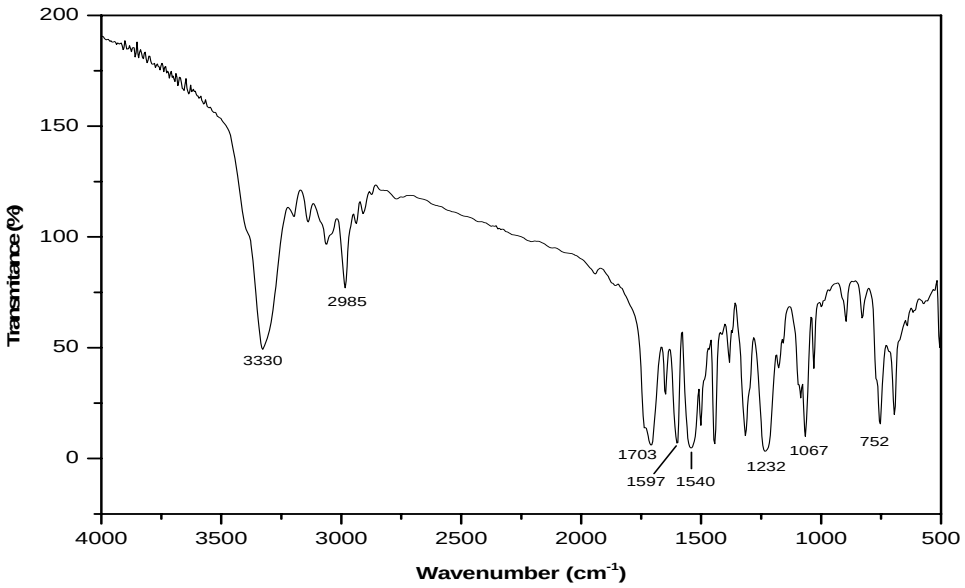
^{1}H NMR Spectrum of compound **2b** ($CDCl_3$, 200 MHz)



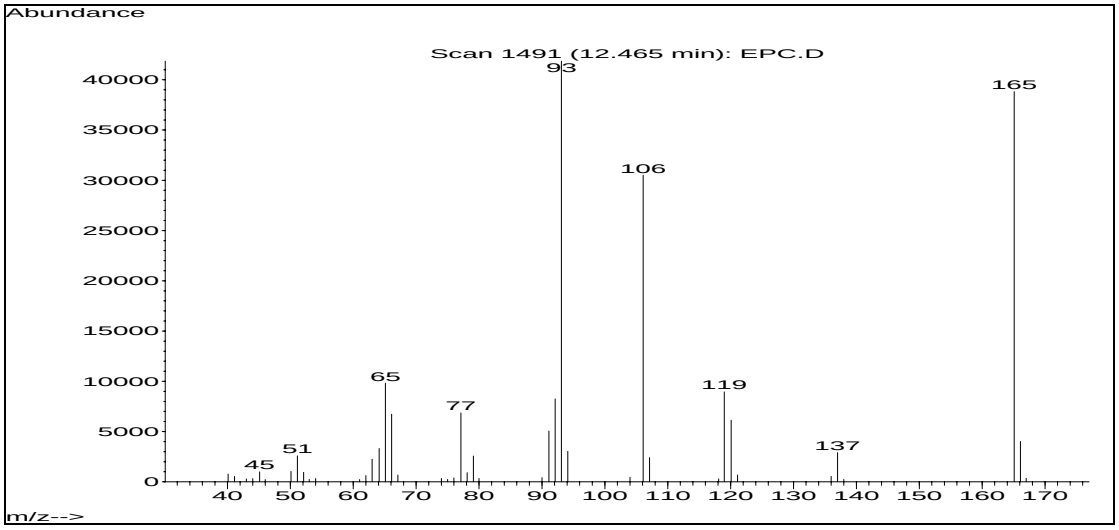
^{13}C NMR Spectrum of compound **2b** ($CDCl_3$, 500 MHz)



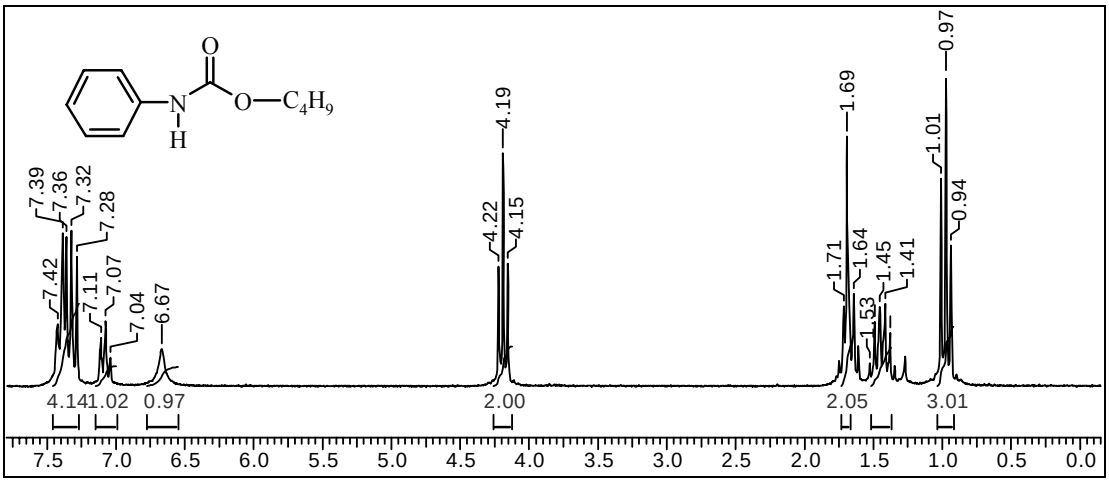
DEPT Spectrum of compound **2b** ($CDCl_3$, 500 MHz)



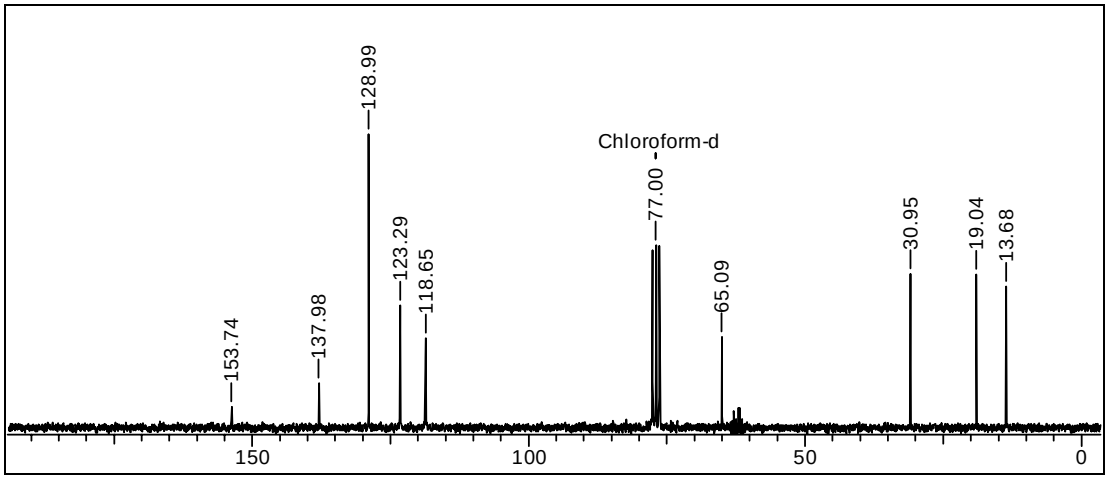
IR Spectrum of compound **2b** (KBr)



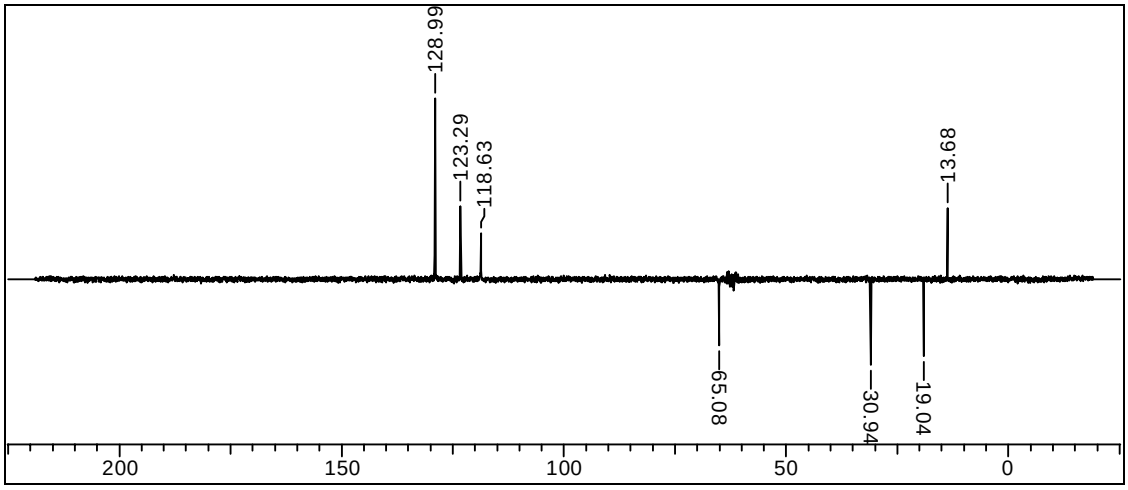
GC-MS Spectrum of compound **2b** (70 eV, EI)



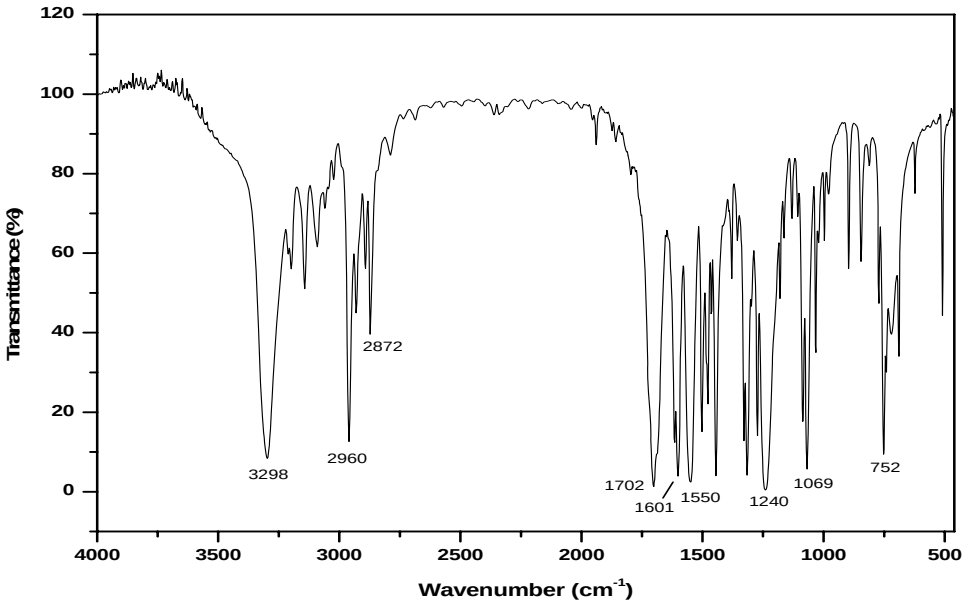
^{1}H NMR Spectrum of compound **2c** ($CDCl_3$, 200 MHz)



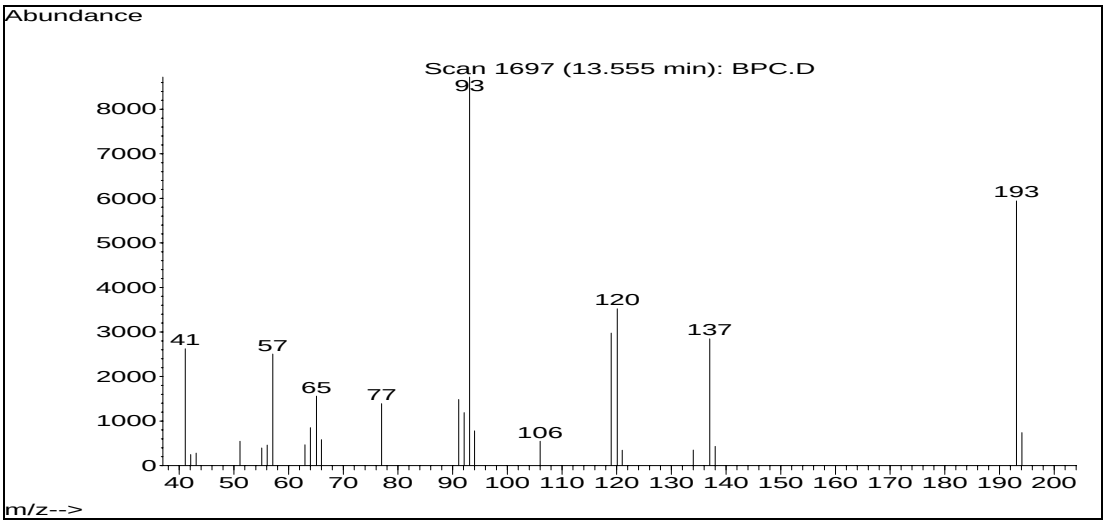
^{13}C NMR Spectrum of compound **2c** ($CDCl_3$, 500 MHz)



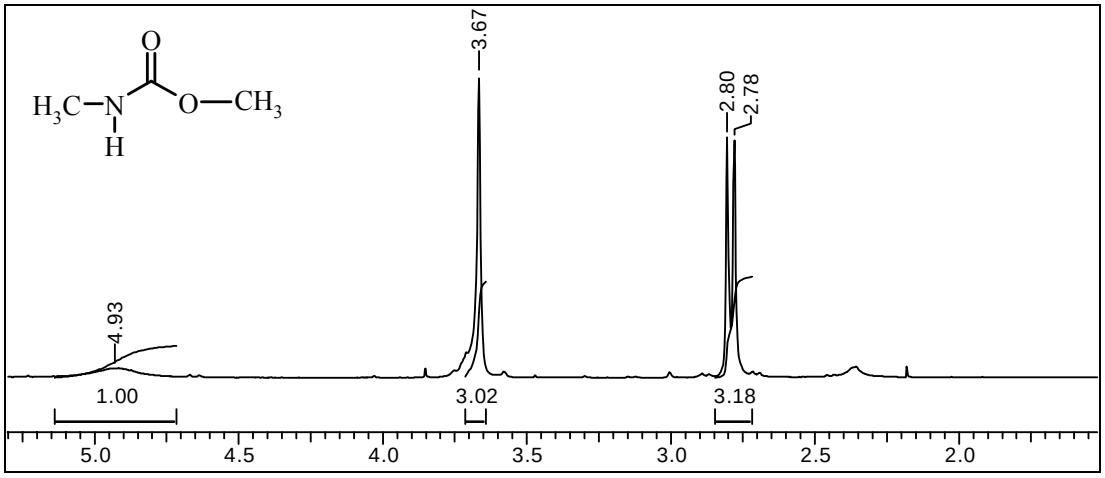
DEPT Spectrum of compound **2c** ($CDCl_3$, 500 MHz)



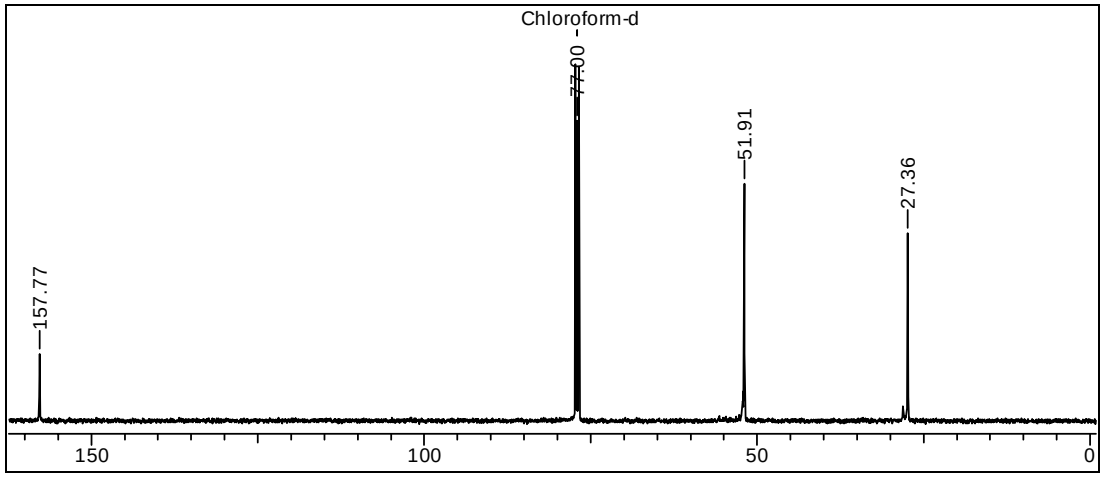
IR Spectrum of compound **2c** (KBr)



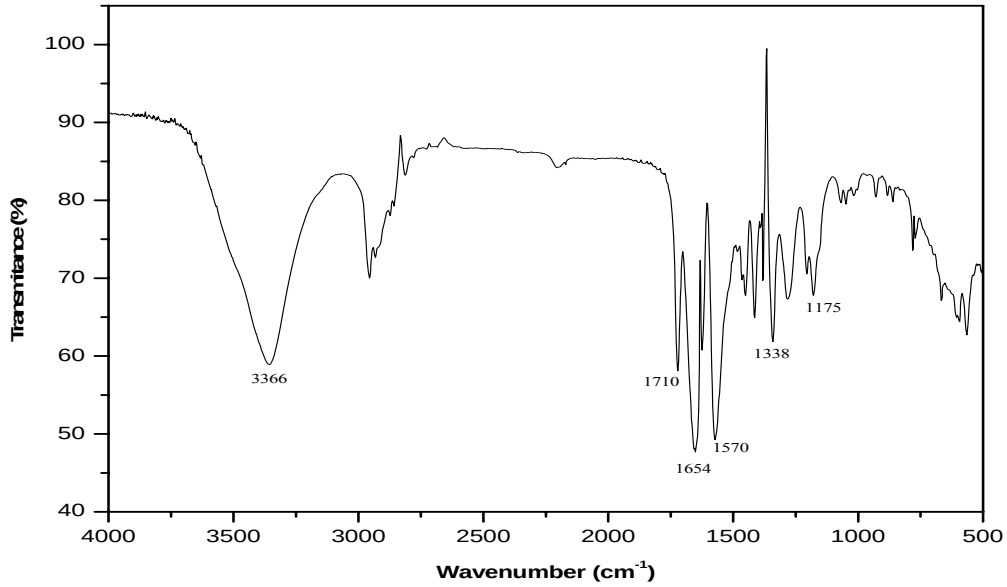
GC-MS Spectrum of compound **2c** (70 eV, EI)



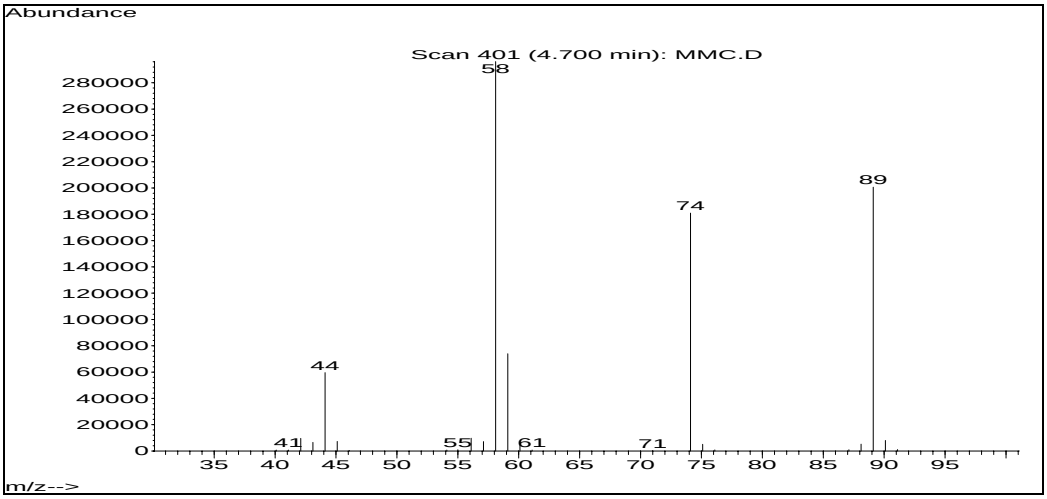
^{1}H NMR Spectrum of compound **3a** ($CDCl_3$, 200 MHz)



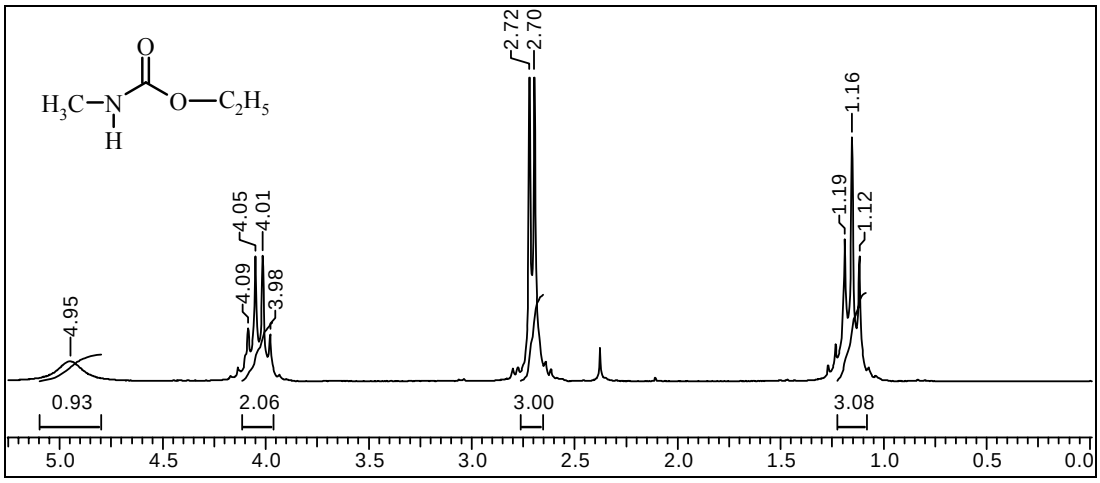
^{13}C NMR Spectrum of compound **3a** ($CDCl_3$, 200 MHz)



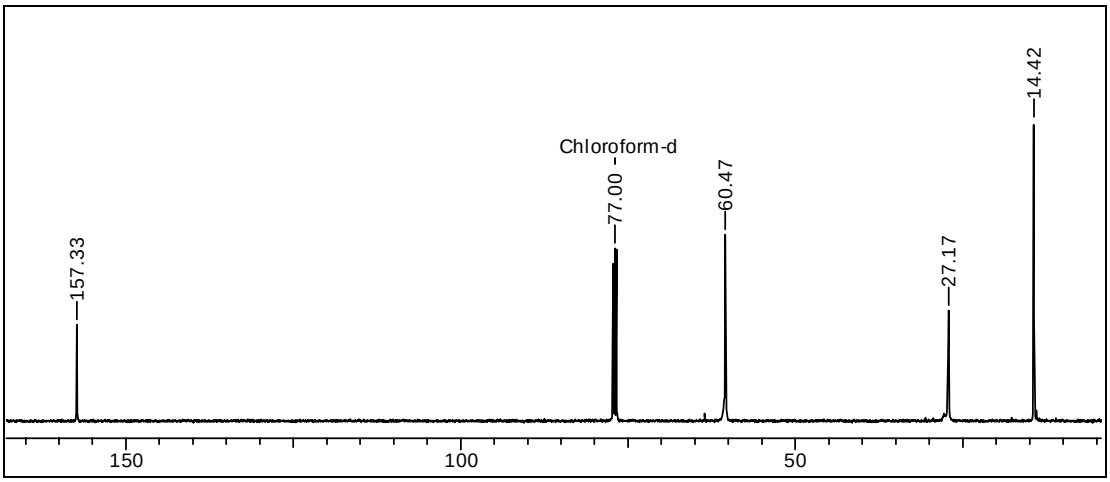
IR Spectrum of compound **3a** (film)



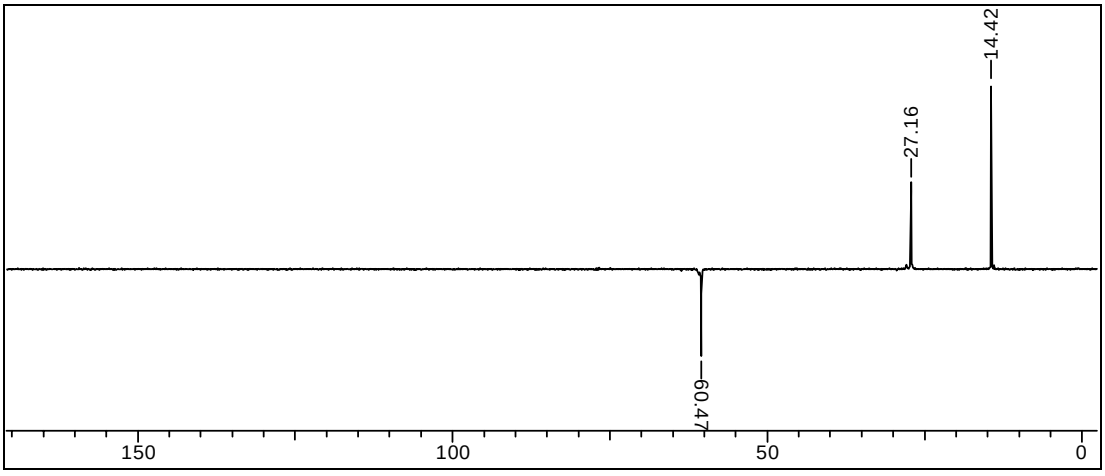
GC-MS Spectrum of compound **3a** (70 eV, EI)



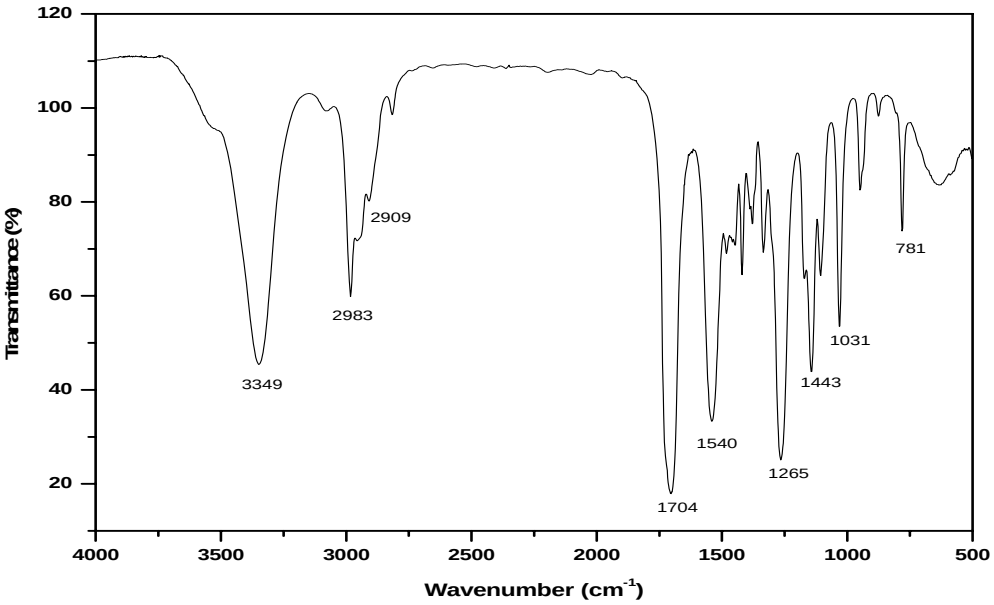
^{1}H NMR Spectrum of compound **3b** ($CDCl_3$, 200 MHz)



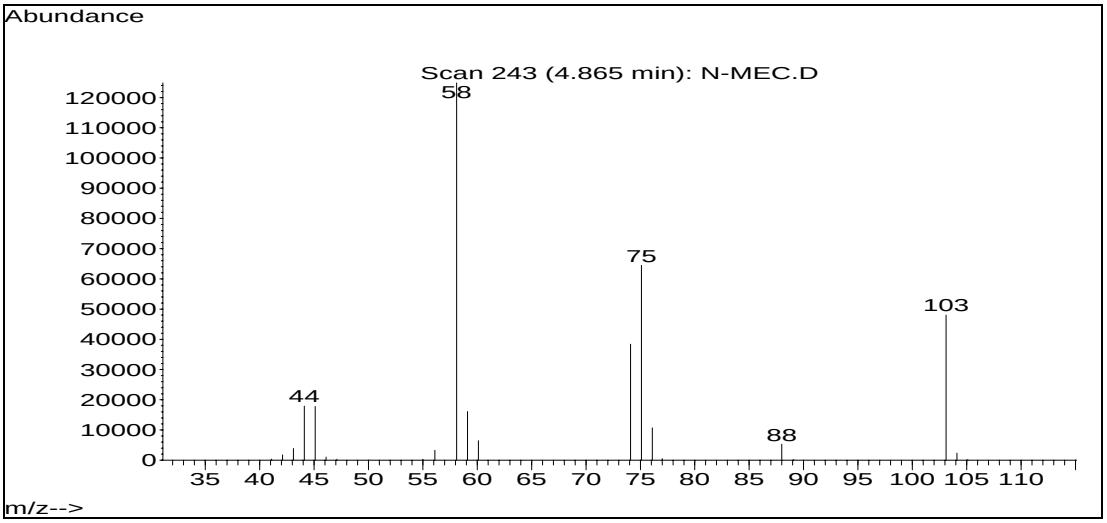
^{13}C NMR Spectrum of compound **3b** ($CDCl_3$, 500 MHz)



DEPT Spectrum of compound **3b** ($CDCl_3$, 500 MHz)



IR Spectrum of compound **3b** (film)



GC-MS Spectrum of compound **3b** (70 eV, EI)

Chapter 3

Synthesis of *N*,*N*-dimethyl anilines from Aromatic Amines and Dimethyl Carbonate

3.1. INTRODUCTION

N,*N*-dimethyl anilines are valuable intermediates in the synthesis of pharmaceuticals, agrochemicals and dyestuffs as well as fine chemicals such Vanillin, Michler's ketone etc. They are also used as solvents and additives in the production of synthetic rubber.[1] *N*,*N*,*N'N'*-tetramethyl-1,4-phenylene diamine is used in the bio-medical field as a reagent known as Wruster's blue.[2]

The liquid phase alkylation processes for synthesis of *N*,*N*-dimethyl aniline (NNDMA) was commercialized in 1866 in which aniline and methanol were heated in presence of sulfuric acid at 478 K under pressure.[3] In general practice, dimethyl sulfate and methyl iodide are used as methylating agent in stoichiometric amount producing salts in large quantities. These processes lead to problems like, corrosion, high toxicity and cause pollution to environment due to neutralization of the acids and undesired by-products. Although in the last decades attempts were made to develop alternative processes based on environmentally acceptable starting materials such as methanol as the alkylating agent and solid acid as recyclable catalysts.[4] The process still requires high temperatures typically in the range 573 to 623 K and the yield of dialkylated product is very low (in the range of 12–40%).[5] A vapor phase continuous process for the production of NNDMA from aniline and methanol has been described using alumina based solid acid catalyst, wherein ~ 86% yield of *N*,*N*-dimethyl aniline has been reported.[6] Recently, it has been shown that co-crystallized RHO-zeolite X (FAU) catalyst is highly active for vapor phase *N*-alkylation of aniline by methanol and in this case a maximum yield of ~ 85% NNDMA is reported.[7]

In recent years, dimethyl carbonate (DMC) has emerged as a benign methylating agent in organic synthesis.[8] Although it is less reactive than methyl iodide and dimethyl sulfate, it has the advantage of being much less toxic. DMC has been successfully used to introduce a methyl group at the α-position of the aryl acetonitriles[9] and methyl aryl acetates.[10] It has also been used for *N*-alkylation of aromatic amines and imidazoles.[11] The vapor phase *N*-alkylation of aniline using DMC as alkylating agent was investigated extensively.[12] In particular Fu and Ono reported high yield of *N*-methyl aniline (NMA) with selectivity ~ 92% using Faujasite Na-X as a catalyst at 423 K, while at 513 K temperature *N, N*- dimethyl aniline was produced with selectivity > 95% with 100% aniline conversion.[12b] Sreekumar et al. performed vapor phase alkylation of aniline using DMC over hydrotalcite[12c] and $Zn_{1-x}Co_xFe_2O_4$ catalyst[13] at 573 K however, selectivity for NNDMA was very poor 22%. *N*-alkylation of aniline using organic carbonate in the presence of metallosilicates, Faujasite, EMT and beta alkaline zeolite as catalysts was also reported in which selectivity of NNDMA obtained was in the range of 50-75%.[5c]

Tundo and co-workers[14] reported the liquid phase *N*-methylation of anilines using DMC as an alkylating agent and Faujasite X or Y zeolite as a catalyst. Their results indicated that at a temperature of 363-453 K, *N*- methyl aniline was produced selectively in 96% yield with only traces of dimethyl derivative. While, Nagaraju and Kuriakose reported the reaction of aniline and DMC over V-$AlPO_4$ or Co-$AlPO_4$ catalyst gave biphenyl urea as a major products.[15] A patent filed by Anic, S.P.A. described synthesis of NNDMA from MeI and DMC under pressure at 421 K, with 85% yield of NNDMA.[16] Shen and Jiang showed that diphenylammonium triflate as an excellent catalyst for selective synthesis of *N,N*-dimethyl anilines.[17] Recently Selva et al.[18] showed selective

N,*N*-dimethylation of primary aromatic amines using unsymmetrical methyl alkyl carbonate in presence of phosphonium salt. Jenner and Taleb[19] investigated *N*-alkylation of nitro arenes using methyl formate as a hydrogenating as well as alkylating agent. In this case, $Ru_3(CO)_{12}$ acted as a hydrogenation catalyst while further *N*-alkylation of reduced nitro derivative was achieved by the onium salts. A maximum of 97% yield of dialkylated product was obtained at 493 K. Dehmlow et al.[20] examined the *N*-alkylation of anilines by alkyl halides under PTC conditions (onium salt and alkali hydroxide), but the maximum yield of dialkylated product obtained was only 22%.

Thus, most of the previous reports on synthesis of *N*,*N*-dialkylated anilines suffer from several techno-ecological problems. For example (a) Conventional alkylating agents (MeI, DMS etc.) are corrosive, toxic and not good from environmental point of view, (b) Alcohols as alkylating agents are effective only at higher temperatures (> 523 K) besides the formation of side products such as toluidines due to ring alkylation, (c) The results on *N*-alkylation of anilines with organic carbonates using solid catalyst indicate that, mono alkylated products are formed selectively in the liquid phase reaction as compared to dialkylated products. While, dialkylated products formed selectively under vapor phase conditions and require very high temperature > 513 K. The *N*,*N*-dimethylation of aromatic amines under batch condition is not extensively studied, (d) Due to the closeness of the boiling points of aniline (457 K), *N*-methyl aniline (469 K) and *N*,*N*-dimethyl aniline (466-465 K), it is extremely difficult to separate these compounds into pure components by distillation. The normal method of separation is the acetylation of crude product, which fixes aniline and NMA chemically. In this way, however, the recovery of the by-products and purification of the NNDMA consumes substantial

amounts of energy and expensive chemicals. Therefore, it is most desirable to produce selectively NNDMA in high yield.

In view of this, objective of the present work was to develop new catalytic system for selective synthesis of *N*,*N*-dimethyl anilines by *N*-alkylation of primary aromatic amines using dimethyl carbonate. In this chapter, experimental results on *N*-alkylation of aromatic amines by dimethyl carbonate using various onium salts and heterogeneous catalysts such as quaternary salt immobilized on silica gel and ionic liquid immobilized on silica gel are demonstrated. Various aspects such as, process parameters and effect of water on product selectivity and catalyst recycle have been studied.

3.2. EXPERIMENTAL SECTION

3.2.1. MATERIALS

Aniline, substituted aromatic amines, dimethyl carbonate (DMC) and diethyl carbonate (DEC) were purchased from S.D. fine chemical ltd. India. Various quaternary salts like; tetramethylammonium bromide (TMAB), tetraethylammonium bromide (TEAB), tetraethylammonium iodide (TEAI), tetrapropylammonium bromide (TPAB), tetrabutylammonium bromide (TBAB), tetrabutylphosphonium bromide (TBPB), diphenyl carbonate and dibutyl tin oxide were purchased from Aldrich chemicals, USA. Materials such as, Cs-Y, Cs-beta, Cs-MCM41, Cs-Na-X, Na-ZSM-5 and K-L already synthesized and well characterized in our laboratory were used as such. n-dibutyl carbonate and Mg-Al Htlc was prepared according to literature procedure (see Chapter 2.2.1.2 & 2.2.1.5). Amines were freshly distilled prior to use.

3.2.2. GENERAL PROCEDURE FOR SYNTHESIS OF *N,N*-DIMETHYL ANILINE DERIVATIVES

N-alkylation reactions were carried out in a 50 ml Parr Autoclave made of Hastelloy-C-276. In a typical experiment, weighed quantities of the catalyst, amine, dimethyl carbonate and water were charged into the autoclave. The autoclave was flushed with nitrogen and then pressurized with nitrogen up to 3.4 MPa. Then the contents were heated to the required temperature for 2 h under stirring at 13 Hz. After cooling the reaction mixture to room temperature, the gases were vented off and liquid phase was quantitatively analyzed using gas chromatography. A similar experimental procedure was followed for testing the immobilized ionic liquids and quaternary salts. Details of the liquid phase analysis are given in the section 3.2.3. The products were confirmed by GC-MS analysis.

3.2.3. ANALYTICAL METHODS

Liquid samples were analyzed on a Hewlett Packard 6890 Series GC equipped with auto sampler instrument, controlled by the HP Chemstation software, by using an HP-5 capillary column (30 m x 320 μm x 0.25 μm film thickness, on a 5% phenyl methyl siloxane stationary phase). GC-MS was carried out on Agilent 6890 instrument. Solid state MAS-NMR measurement of the immobilized solid catalyst was carried out on Bruker-AV 500 machine. Elemental analysis of the immobilized solid catalysts was carried out on CHNS-O EA 1108, Elemental analyzer of Carlo Erba Instrument, Italy. DRIFT IR of the immobilized solid catalysts was performed on Perkin Elmer, Spectrum one, FT-IR spectrometer. BET surface area analysis was done on NOVA-2000 Version 8,

Instrument by nitrogen physisorption. The standard conditions for GC analysis are given in Table 3.1.

Table 3.1. Standard conditions for GC analysis

Parameters	Conditions
Injector (split) temperature	523 K
Flame ionization detector (FID) temperature	573 K
Column temperature (HP-5 capillary column)	318 K–563 K (programmed)
Inlet Pressure (He)	10 psig
Carrier gas (He) flow rate	2.2 ml/min
Split ratio	50:1

The conversion, selectivity, yield, turnover number (TON) and turnover frequency (TOF) were calculated as follows.

$$\%\ Conversion\ of\ aniline = \frac{Initial\ moles\ of\ aniline - Final\ moles\ of\ aniline}{Initial\ moles\ of\ aniline} X\ 100$$

$$\%\ Selectivity\ of\ NNDMA = \frac{No.\ of\ moles\ of\ NNDMA\ formed}{No.\ of\ moles\ NNDMA\ expected\ based\ on\ aniline\ conversion} X\ 100$$

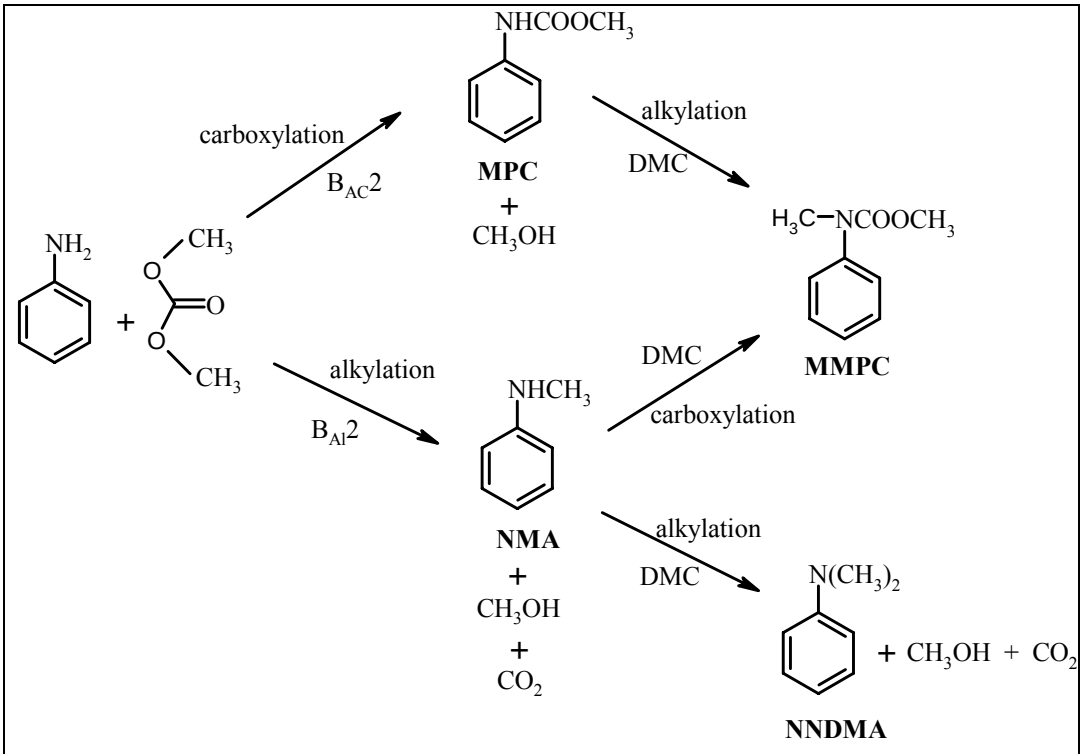
$$\%\ Yield\ of\ NNDMA = \frac{No.\ of\ moles\ of\ NNDMA\ formed}{No.\ of\ moles\ of\ aniline\ charged} X\ 100$$

$$TON = \frac{No.\ of\ moles\ of\ NNDMA\ formed}{No.\ of\ moles\ of\ catalyst\ charged}$$

$$TOF, h^{-1} = \frac{No.\ of\ moles\ of\ NNDMA\ formed}{No.\ of\ moles\ of\ catalyst\ charged\ X\ time\ in\ hours}$$

3.3. RESULTS AND DISCUSSION

In this work, selective *N,N*-dimethylation of primary aromatic amines by dimethyl carbonate as alkylating agent was investigated. Since carbonates posses two electrophilic carbon (alkyl and carbonyl), they may act as both alkylating and carboxylating agents (Scheme 3.1). This reactivity can be often differentiated by the temperature and by the catalyst: below 363 K, carbonates react via $B_{AC}2$ mechanism, whereas over 403 K, both $B_{AC}2$ and $B_{Al}2$ pathways may coexist. Thus, the complexities arising due to DMC in the reaction for selective synthesis of *N,N*-dimethyl aniline were investigated by studying process parameters.



Scheme 3.1

3.3.1. SYNTHESIS OF *N,N*-DIALKYL ANILINES USING HOMOGENEOUS ONIUM SALTS

3.3.1.1. Preliminary experiments for catalyst screening

Various homogeneous as well as heterogeneous catalysts were screened for the *N*-alkylation reaction of aniline and dimethyl carbonate and results are presented in Table 3.2. It was observed that solid acid / base catalysts such as MgO, hydrotalcites, clays and zeolites were not selective catalysts for synthesis of NNDMA (entry 1-10). Homogeneous basic catalyst e.g. dibutyl tin oxide showed more activity towards carboxylation reaction to give carbamate as major product rather than NNDMA (entry 11). Whereas, with tetraethyl ammonium bromide (TEAB) as a catalyst, 76% yield of NNDMA was obtained with 24% yield of carbamate (entry 12). On the other hand, *N*-alkylation under biphasic (organic/aqueous) conditions with TEAB catalyst gave selectively only *N*-alkylated amines, wherein carbamates were not detected (entry 13). Under biphasic conditions, large amount of DMC was hydrolyzed resulting in a poor selectivity of NNDMA based on DMC conversion. These results were however encouraging, since in the presence of water, selectively to *N*-alkylated products were formed (yield of NMA 16% and NNDMA 78%, entry 13). But under these conditions complete conversion of aniline was not achieved. However, methyl *N*-phenyl carbamate (MPC) and methyl *N*-methyl-*N*-phenyl carbamate (MMPC) were completely absent. This clearly showed that, water played a key role in improving selectivity of *N*-alkylated products. Therefore the role of water in *N*-alkylation of aniline was also investigated as this effect was thought to be vital for the understanding of *N*-alkylation.

Table 3.2. Screening of catalysts for *N*-alkylation of aniline

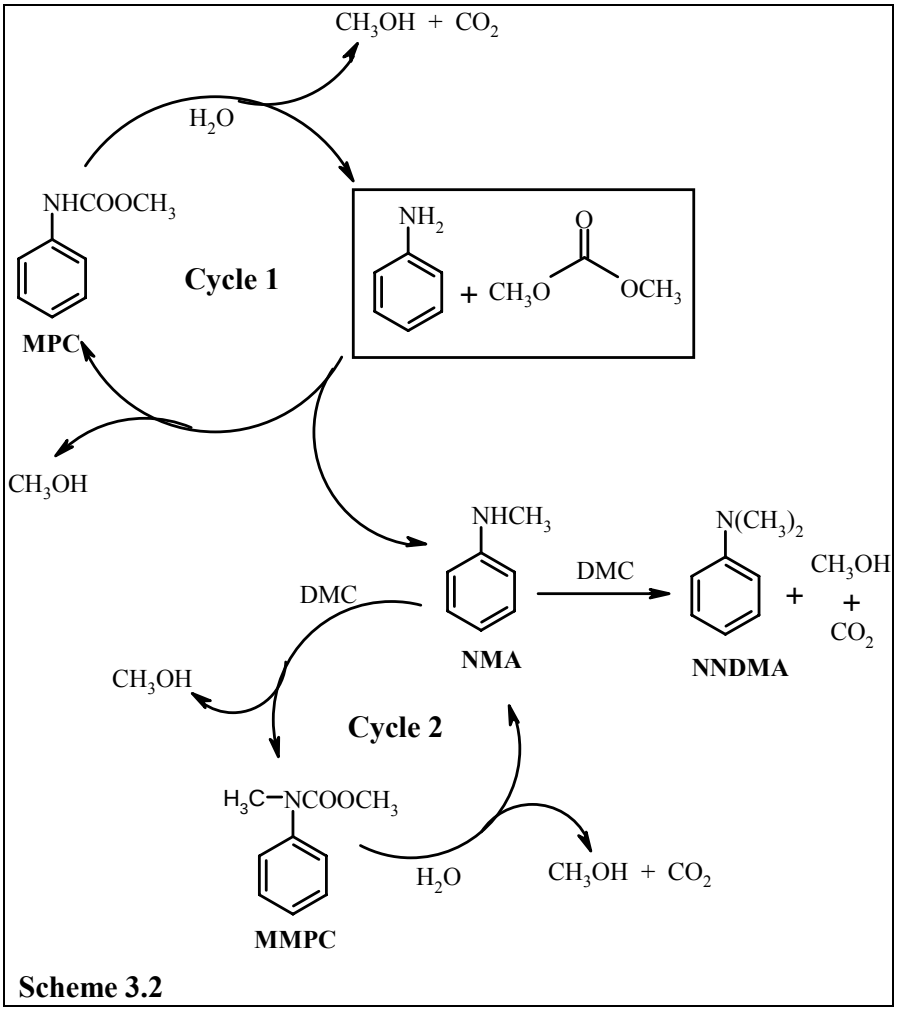
Entry	Catalyst (g)	Time, (h)	Aniline conversion, (%)	Yield[a], (%)		
				MPC	NMA	NNDMA
1	MgO (0.25)	2	nil	-	-	-
2	Mg-Al Htlc (0.25)	2	5	0	5	0
3	H-mordenite (1)	2	15	4	8	3
4	K^+ silica (1)	2	7	3	4	0
5	K-L (1)	2	46	7	28	11
6	Na-ZSM-5 (1)	2	10	0	8	1
7	Cs-Na-X (1)	2	100	0	40	60
8	Cs-Y (1)	2	100	0	85	15
9	Cs-beta (1)	2	26	10	12	4
10	Cs-MCM-41 (1)	2	26	13	11	2
11	Bu_2SnO (0.45)	2	50	43	2	5
12	$(Et)_4NBr$ (1.5)	2	100	8 (16)[b]	-	76
13[c]	$(Et)_4NBr$ (1.5)	2	94	0	16	78

Reaction conditions: aniline, 16.1mmol; DMC, 190 mmol; T., 423 K; N_2 pressure, 3.4 MPa; Agitation speed, 13 Hz; reaction volume, 20 ml; [a] yields were determined by GC based on aniline conversion; [b]MMPC; [c]biphasic conditions (DMC, 100 mmol; H_2O, 560 mmol) and T., 443 K.

3.3.1.2. Role of water

The effect of water on conversion of aniline and yields of *N*-alkylated products (NNDMA, NMA) and carbamate (MMPC) is shown in Figure 3.1. In absence of water the yield of NNDMA obtained was 85% and appreciable amount of MMPC was formed (15%). Addition of water to the system remarkably improved the yield of NNDMA to almost 99.8% with traces of NMA (0.2%, yield) while MMPC was completely absent (Figure. 3.1). At higher concentration of water, the biphasic conditions were approached decreasing the yield of NNDMA (see also preliminary experiment for catalyst screening section, 3.1.1.1). Thus, there exists an optimum quantity of water to be added to the system in order to maximize the selectivity to *N*-alkylated products. Therefore, experiments were carried out by adding precalculated water to the system. Water played a

key role in the selective synthesis of *N*,*N*-dimethyl aniline and in hydrolysis of carbamates. For example hydrolysis of DMC, methyl *N*-phenyl carbamate (MPC) and methyl *N*-methyl *N*-phenyl carbamate (MMPC) are known to give methanol, CO_2, aniline and *N*-methyl aniline (Scheme 3.2).



Scheme 3.2

A blank experiment was carried out without aniline under standard reaction conditions and it was observed that 50% of DMC was hydrolyzed to methanol and CO_2. Hydrolysis of DMC is an unwanted reaction as it reduces DMC based selectivity of NNDMA. While, hydrolysis of both MPC and MMPC to aniline and to *N*-methyl aniline respectively is a welcome reaction as it helps to increase the selectivity of *N*-alkylation

(Scheme 3.2, cycle 1 & 2). Particularly, hydrolysis of MMPC to NMA is important since it was observed earlier that in the absence of water this carbamate decreased the selectivity of *N*-alkylated products (also discussed later). Once *N*-methyl aniline was produced, further alkylation by DMC gave NNDMA (Scheme 3.2).

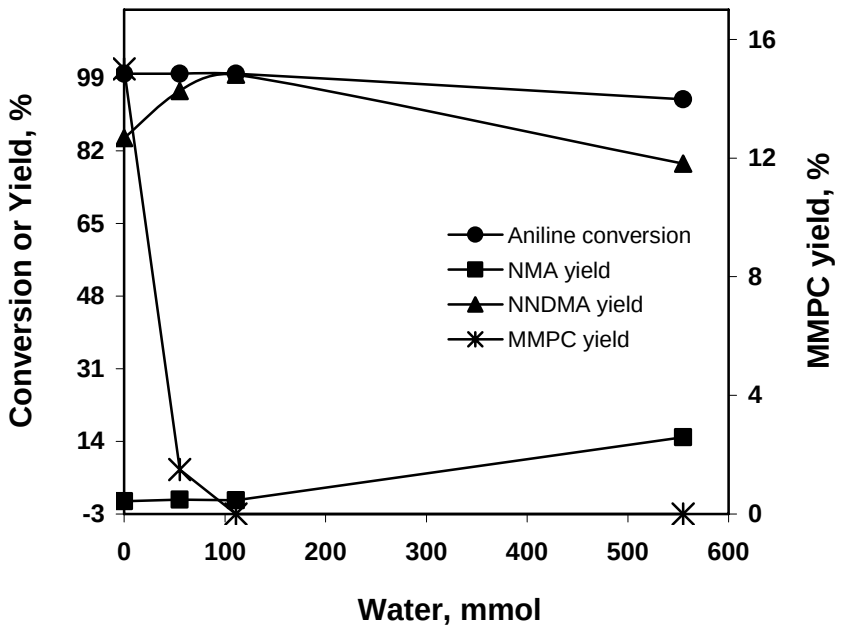


Figure 3.1. Effect of water on NNDMA yield

<u>Reaction conditions</u>: aniline, 10.7 mmol; DMC, make-up to 20 ml; TEAB catalyst, 3.57 mmol; T., 443 K; N_2 pressure, 3.4 MPa; Time, 2 h, Agitation speed, 13 Hz; Yields were determined by GC and are based on aniline conversion.

3.3.1.3. Screening of onium salts as catalyst

Several onium salts as catalysts were screened and the results are presented in Table 3.3. It was observed that 100% aniline conversion was achieved in all the cases with selectivity > 95% for the dialkylated products within 2 h. The variation in selectivity with different onium salts as catalyst was only marginal, while tetra methyl and ethyl ammonium bromides favored the most selective formation of NNDMA with selectivity

close to 100%, however tetra butyl ammonium chlorides was less active and showed poor selectivity for NNDMA (50%, entry 5). Phosphonium salt showed marginal improvement in the yields of NNDMA over ammonium salts (entry 4 & 8) and can be a substitute for ammonium salts. It was further observed that hindered onium salt e.g. hexaethyl gaunidinium bromide also showed excellent activity towards *N*-alkylation (entry 6). In order to ascertain the activity trend in onium salts, conversion and yields were monitored at shorter contact time (0.5 h). No particular trend was observed for screened onium salts as catalyst and poor selectivity for NNDMA was obtained in the range of 40-50%. The lower selectivity for NNDMA in the initial period was found to be due to interaction of aniline with onium salt forming an activated intermediate of quaternized aniline and due to formation of NMA. To check the possibility of formation of quaternized intermediate of aniline an experiment was performed, in which aniline was treated with $(Et)_4NBr$ without DMC in toluene solvent for 0.5 h under same reaction conditions similar to that mentioned for Table 3.3. This experiment showed ~ 18% aniline conversion and no *N*-alkylated products were detected (entry 9). A direct comparison of catalyst activities of quaternary salts is difficult under experimental conditions due to the substrate interaction with catalyst to form activated adduct in the initial period (0.5 h). In homologous series of quaternary ammonium bromides, the formation of carbamate as a side product increased from methyl to butyl (entry 1 to 4). This effect is probably due to the fact that $[(n\text{-}C_4H_9)_4N]Br$ is more lipophilic than either methyl or ethyl quaternary ammonium bromides[21] and hence not as efficient in hydrolyzing carbamates (which essentially proceeds in hydrophilic media) to amines, thus decreasing selectivity of *N*-alkylated products.

Table 3.3. Screening of onium salts for *N*-alkylation of aniline

Entry	Onium salt	Aniline conversion, (0.5h), %	NNDMA (0.5 h)		NMA (0.5 h)		Other [b] (0.5 h), %
			Sel., %	Yield[a], %	Sel., %	Yield[a], %	
1	$(Me)_4NBr$	100 (82)	98.8 (39.6)	98.8 (32.2)	1.2 (7.3)	1.2 (6)	Nil (nil)
2	$(Et)_4NBr$	100 (97.1)	99.8 (53)	99.8 (51.4)	0.2 (5.5)	0.2 (5.3)	Nil (nil)
3	$(n\text{-}Pr)_4NBr$	100 (98)	98 (55.5)	98 (54.2)	0.5 (3.9)	0.5 (3.8)	1.5 (nil)
4	$(n\text{-}Bu)_4NBr$	100 (98.1)	96 (49.5)	96 (48.6)	0.2 (4)	0.2 (3.9)	3.8 (0.5)
5	$(n\text{-}Bu)_4NCl$	88.12 (61)	50 (40.9)	44.13 (25)	17.24 (14.7)	15.2 (9)	3.5 (1)
6	$HegBr^c$	100 (97.5)	96.8 (47.5)	96.8 (46.2)	0.2 (5.9)	0.2 (5.7)	3 (1.0)
7	$(Et)_4NI$	100 (100)	98 (57.2)	98 (57.2)	0.2 (nil)	0.2 (nil)	1.8 (0.8)
8	$(n\text{-}Bu)_4PBr$	100 (97.4)	97.8 (51.1)	97.8 (49.8)	0.3 (4.9)	0.3 (4.8)	1.9 (0.6)
9	$(Et)_4NBr^d$	(18)	0	0	0	0	0

Reaction conditions: aniline, 16.1 mmol; DMC, 190 mmol; Catalyst, 3.57 mmol; H_2O, 110 mmol; T., 443 K; N_2 pressure, 3.4 MPa; Time, 2 h; Agitation speed, 13 Hz; reaction volume, 20 ml; [a] yields were determined by GC based on aniline conversion; [b] MPC, MMPC; [c] Hexaethyl guanidinium bromide; [d] in absence of DMC

3.3.1.4. Effect of substrate

Several substituted anilines such as toluidine, chloro anilines, nitro aniline and anisidine were investigated to see the reactivity of substrates towards *N*-alkylation by DMC (Table 3.4). Excellent yields of dialkylated products were obtained in most of the screened amines except *p*-nitro and *o*-chloro anilines (entry 5 & 7). Since the *N*-alkylated products are formed by the nucleophilic substitution of anilines on DMC, electron donating or withdrawing substituents on aniline are expected to increase or decrease the nucleophilic character of aniline respectively. Although substituted anilines followed the

expected reactivity pattern that is based on the nucleophilicity of anilines, the effect was not very pronounced for electron donating substituents but at the same time steric hindrance of these substituents to NH_2 group was dominating the reactivity of anilines. For example *o*-chloro aniline showed lower conversion and poor selectivity to respective dialkylated product (entry 5). In *p*-nitro aniline, -NO_2 is very strong electron withdrawing group and having '–R' effect which decreases nucleophilic character of aniline, showing poor conversion and selectivity to dialkylated product (entry 7). The alkylated product of 1,4 phenylene diamine (entry 8) has a special importance as a reagent and excellent yield of *N*,*N*,*N*`,*N*`- tetramethyl 1,4 phenylene diamine was obtained.

Table 3.4. Synthesis of *N*,*N*-dimethyl anilines using TEAB catalyst

Entry	Amine	Dialkyl yield[a], (%)	Monoalkyl yield[a], (%)	Side products[b] yield[a], (%)
1	$C_6H_5NH_2$	99.8	0.2	0
2	*p*-CH_3-$C_6H_4NH_2$	99.5	0	0.5
3	*p*-Cl-$C_6H_4NH_2$	98.5	0.3	1.2
4	*m*-Cl-$C_6H_4NH_2$	98.5	0.4	1.1
5	*o*-Cl-$C_6H_4NH_2$	62.6	30.2	0.8
6	*p*-CH_3O-$C_6H_4NH_2$	99.6	0	0.4
7	*p*-NO_2-$C_6H_4NH_2$	35.9	27	7
8	*p*-NH_2-$C_6H_4NH_2$	98	0	2

Reaction conditions: aniline, 16.1 mmol; DMC, 190 mmol; TEAB, 3.57 mmol; H_2O, 110 mmol; T., 443 K; N_2 pressure, 3.4 MPa; Time, 2 h; Agitation speed, 13 Hz; reaction volume, 20 ml; [a] yields were determined by GC based on aniline conversion; [b] N-carbamates.

3.3.1.5. Effect of solvent

Five different solvents were screened with a wide range of variation in their dielectric constants (ε) to see the effect of solvent on catalyst activity and selectivity to *N*-alkylated products. These results are presented in Figure 3.2. The results on solvent

screening indicated that as dielectric constant (ε) of a solvent increased, conversion and yield of NNDMA passed through an optimum value for ε. The bell shape of the graph (for activity and yield) showed that a maximum of 78% yield of NNDMA was obtained which corresponds to a value of dielectric constant (ε^{25}) = 7.2 (using triglyme as solvent) and at two extremes of this graph lie xylene having $\varepsilon^{25} = 2.25$ and methanol having $\varepsilon^{25} = 32.6$ with NNDMA yield of 11.7 and 45 respectively and other solvents fell in between these two extremes. It was observed that solvents such as *p*-xylene and toluene form a biphasic system in the presence of water and TEAB catalyst was partitioned in two phases decreasing the availability of catalyst in the organic phase. The depletion of catalyst concentration in the organic phase lowered *N*-alkylation rates. The results obtained for triglyme, as a solvent deserves some comments. The *N*-alkylation reaction depends on the nucleophilicity of amines. Factors that increase the nucleophilicity of amines e.g. electron donating groups attached to a ring or nucleophilic environment such as that generated by solvents having basic groups or atoms such as N or O, help to increase it's reactivity.[22] Triglyme has an open chain polyether structure with basic oxygen atoms, and is a perfect solvent capable of inducing nucleophilic environment around hydrogen of amine thus generating reactive (RNH-), which on further reaction with DMC produces *N*-methylated products. This is a probable explanation, however, similar effects have been observed earlier.[22] The results clearly showed that the solvent played an important role in activation (or deactivation) of substrates, but dielectric constant alone did not explain this effect. The effect of DMC, as a solvent ($\varepsilon^{25} = 3.1$) could not be compared, as DMC was also one of the reactants, however, DMC worked as an excellent solvent and due to its benign nature was selected for further studies.

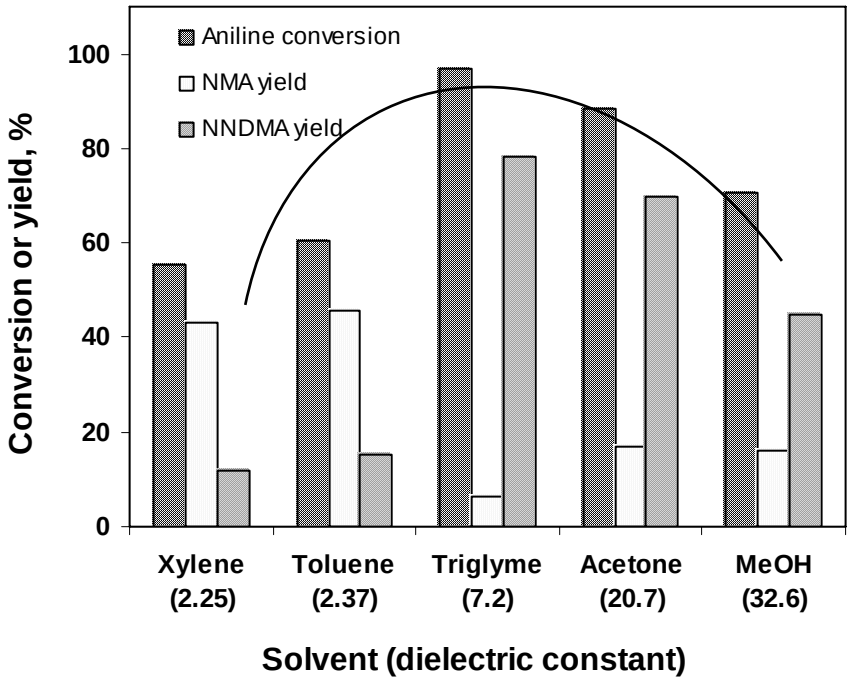


Figure 3.2. Effect of solvent on NNDMA yield

Reaction conditions: aniline, 10.7 mmol; DMC, 32.2 mmol; TEAB catalyst, 2.38 mmol; H_2O, 111 mmol; solvent, 14 ml; T., 443 K; N_2 pressure, 3.4 MPa; Time, 2 h, Agitation speed, 13 Hz; Total volume, 20 ml; Yields were determined by GC and are based on aniline conversion.

3.3.1.6. Efficiency of organic carbonate

The activity of carbonates as alkylating or arylating agents was examined for aniline as a substrate (Figure 3.3). DMC as alkylating agent showed the highest activity followed by ethyl and butyl carbonates, whereas diphenyl carbonate as an arylating agent showed no activity. The results were in complete agreement with the steric hindrance offered by reactive alkyl cation of the carbonate e.g. DMC having (H_3C^+) as methylating cation is the least bulkier as compared to other cations of dialkyl carbonates, and hence shows the highest reactivity. Also from the view point of electronic effects, the expected trend of carbonate reactivity was observed, the methyl cation being the most electrophilic and showed the highest reactivity towards *N*-alkylation. In the reaction of aniline and

diphenyl carbonate, *N*-arylated products were not formed but only hydrolysis of DPC to phenol and CO_2were observed.

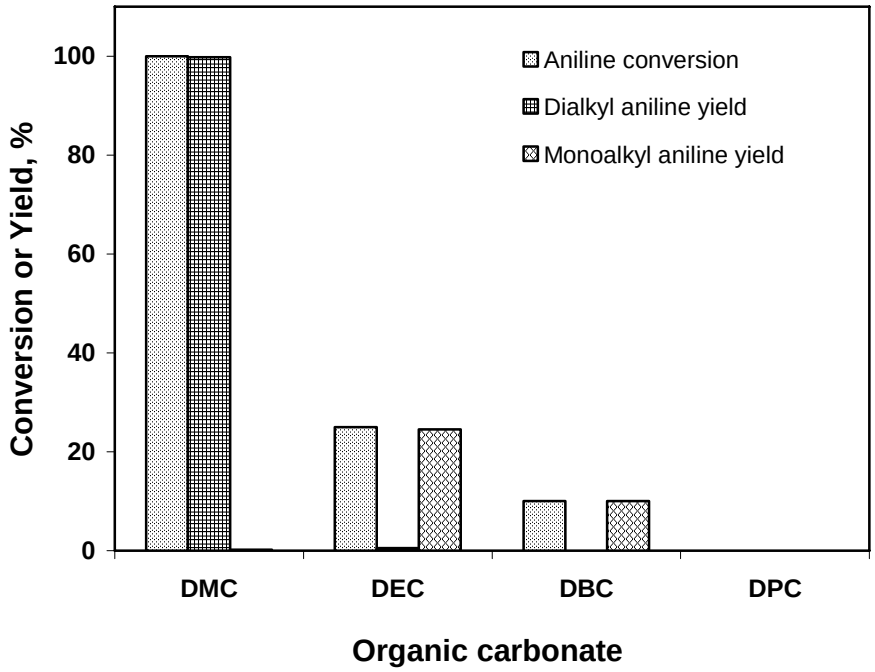


Figure 3.3. Efficiency of organic carbonate as alkylating or arylating agent

Reaction conditions: aniline, 16.1 mmol; organic carbonate, 190 mmol; TEAB catalyst, 3.57 mmol; H_2O, 111 mmol; T., 443 K; N_2 pressure, 3.4 MPa; Time, 2 h, Agitation speed, 13 Hz; Total volume, 20 ml; Yields were determined by GC and are based on aniline conversion.

3.3.1.7. Synthesis of *N,N*-dimethyl aniline (NNDMA)

The effect of reaction conditions was investigated on the most important dialkylated amine, *N,N*-dimethyl aniline. For this purpose, *N*-alkylation of aniline was considered as a model reaction for synthesis of NNDMA. Few experiments were carried out to determine product distribution and material balance in the alkylation of aniline with DMC. Since, DMC was acting as a solvent as well as alkylating agent, aniline was considered as the limiting reactant and on the basis of moles of aniline reacted, NMA and NNDMA formation and DMC consumed were tallied. A complete conversion of aniline

was achieved with concurrent formation of *N*-alkylated products and correspondingly DMC was also consumed although in about 20% excess than the stoichiometric quantities that were required based on aniline consumption, indicating that DMC based selectivity was reduced due to formation of side products arising from hydrolysis of DMC. This is evident from a typical experiment (Table 3.3, entry 2) in which, aniline conversion was 100% with 99.8% selectivity of NNDMA and 0.2% selectivity for NMA formation on the basis of aniline converted and 83.6% selectivity of NNDMA and 0.16% selectivity for NMA on basis of DMC converted was observed at the end of two hours of reaction time. In the present case, both the reactants (amine and carbonate) were infinitely soluble under reaction conditions offering a homogeneous liquid phase. However, experiments were carried out at different agitation speed, which confirmed that beyond 8.3 Hz, conversion of aniline remained unaffected indicating that mass transfer effects are unimportant. Therefore all the experiments were carried out with agitation speed of 13 Hz.

The effect of different parameters on conversion, selectivity and yield are discussed below:

3.3.1.7.1. Effect of catalyst loading

The effect of catalyst loading on conversion of aniline and selectivity of NMA and NNDMA is shown in Figure3.4. Both conversion of aniline and yield of NNDMA increased with increase in TEAB loading while the yield of intermediate NMA decreased. It can be seen from this plot that higher catalyst concentration was required for the selective formation of NNDMA, this however lowers the TON. In the present case, the product NNDMA was formed via an intermediate NMA and the catalyst was

involved in both the steps and hence expected linear dependency of conversion with catalyst loading was not observed.

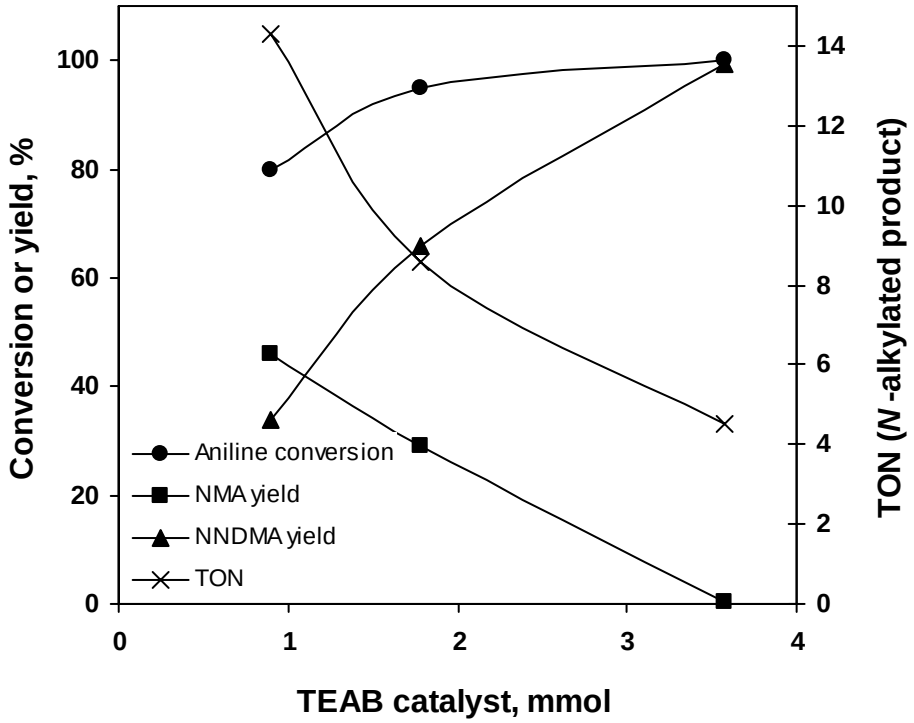


Figure 3.4. Effect of TEAB catalyst loading on NNDMA yield

Reaction conditions: aniline, 16.1 mmol; DMC, 190 mmol; H_2O, 111 mmol; T., 443 K; N_2 pressure, 3.4 MPa; Time, 2 h, Agitation speed, 13 Hz; Total volume, 20 ml; Yields were determined by GC and are based on aniline conversion.

3.3.1.7.2. Effect of temperature

The temperature effect was investigated in the range of 393-443 K and the results are shown in Figure 3.5 as a graph of aniline conversion and yield of alkylated products at different temperatures. The conversion of aniline and NNDMA yield increased sharply with increase in temperature, while NMA yield diminished with increase in temperature. Temperature plays an important role in alkylation of amines when organic carbonates are used as alkylating agents. Both carboxylation and alkylation of amine is possible depending on the temperature of the reaction. Usually, temperature in the range of 423-

473 K was required for selective formation alkylated products.[8a] Side products arising from bromination of aromatic ring or bromination of alkyl group were not detected even at 443 K.

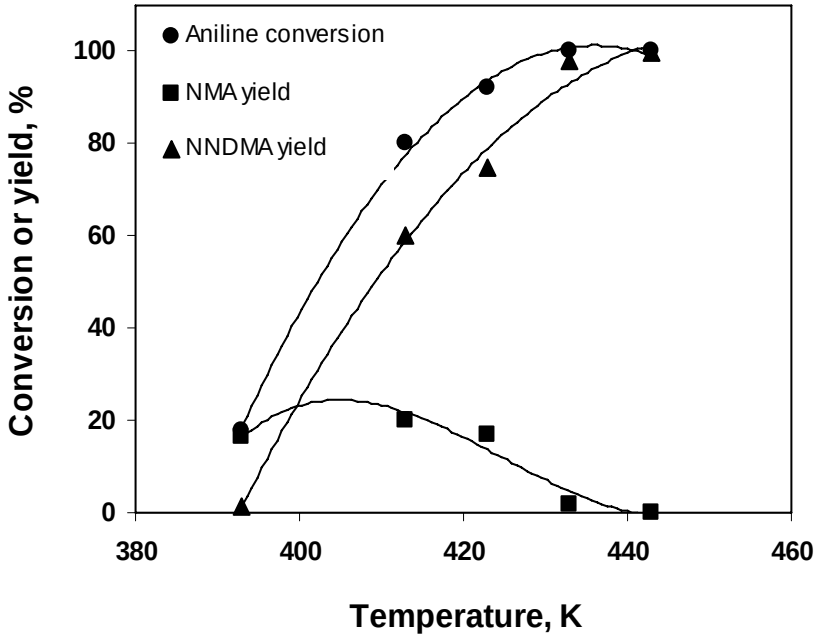


Figure 3.5. Effect of temperature on NNDMA yield

Reaction conditions: aniline, 16.1 mmol; DMC, 190 mmol; TEAB catalyst, 3.57 mmol; H_2O, 111 mmol; T., 443 K; N_2 pressure, 3.4 MPa; Time, 2 h, Agitation speed, 13 Hz; Total volume, 20 ml; Yields were determined by GC and are based on aniline conversion.

3.3.1.7.3. Catalyst recovery and recycling

The catalyst was recovered and recycled by diluting the concentrated reaction crude (free from low boilers such as DMC and methanol) with chloroform and extracting it three times in minimum amount of water (~ 10 ml). The combined aqueous phase was then concentrated by evaporating water to recover TEAB and recycling it with the fresh charge of aniline, DMC and water. The results on catalyst recycle experiments are depicted in the Figure 3.6, which show excellent recycling ability of the catalyst while retaining almost 98 % of its original activity for NNDMA synthesis even after fifth

recycle. The recycling efficiency of the catalyst also confirmed that catalyst degradation arising from brominated products (brominated amines, alkyl bromides etc.) was absent.

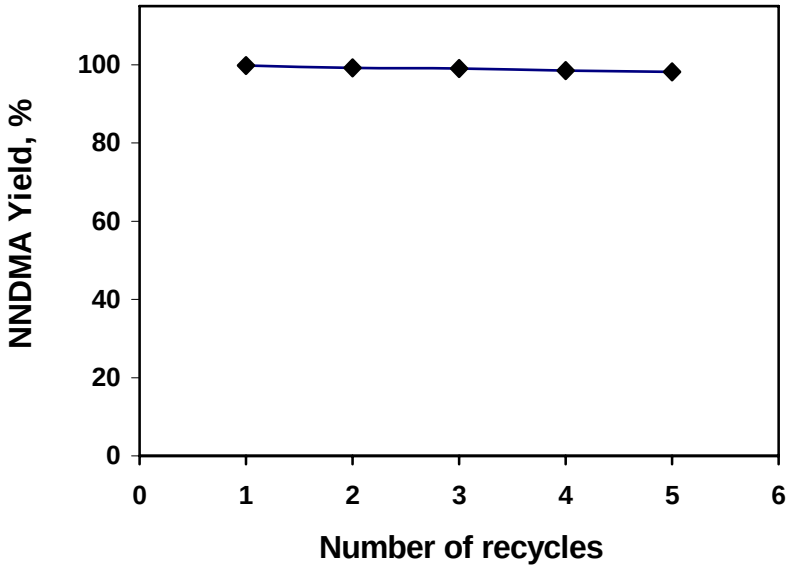


Figure 3.6. TEAB catalyst recycles study

Reaction conditions: aniline, 16.1 mmol; DMC, 190 mmol; TEAB catalyst 3.57 mmol; H_2O, 111 mmol; T., 443 K; N_2 pressure, 3.4 MPa; Time, 2 h, Agitation speed, 13 Hz; Total volume, 20 ml; Yields were determined by GC and are based on aniline conversion.

3.3.1.8. Networking of *N*- alkylation reaction

N-alkylation of aniline by DMC as an alkylating agent produces carbamates and alkylated products depending on the reaction conditions (temperature and water). Carbamates such as methyl *N*-phenyl carbamate (MPC) and methyl *N*-methyl *N*-phenyl carbamate (MMPC) can form via two routes and their inter convertibility into amines via hydrolysis is possible (Scheme 3.2). Moreover, possibility of formation of NMA and DMC via hydrogen transfer reaction between MMPC and methanol (formed during reaction) can not be ruled out under our experimental conditions (see Equation 3.1).[14a]

$$\underset{\textbf{MMPC}}{PhNCH_3COOCH_3} + CH_3OH \longrightarrow PhNHCH_3 + \underset{\textbf{NMA}}{} \underset{\textbf{DMC}}{CH_3OCOOCH_3} \qquad (3.1)$$

To clarify these issues, diagnostic experiments were carried out and these results are presented in Table 3.5. Reaction of MPC with DMC in absence of water produced only MMPC (entry 1), while in the presence of water, a similar experiment showed 50% conversion of MPC to NNDMA (50% yield, entry 2), indicating that hydrolysis of MMPC produced NNDMA via NMA alkylation (Scheme 3.2). In the absence of water, MMPC accumulated in the system, as it did not have active hydrogen atom for further reaction with DMC. Similar reactions were carried out either with NMA or aniline as a substrate with DMC gave NNDMA and MMPC in the absence of water and the same reaction in presence of water gave selectively only NNDMA (entry 3-6). Reaction of aniline or MMPC with methanol under the experimental conditions did not give alkylated anilines indicating that alkylation using methanol was not facile (entry 7 & 8). Similarly reaction of MMPC and DMC did not give alkylated products (entry 9). These experiments conclusively showed that MMPC hydrolysis to NMA was the key reaction in increasing the selectivity of NNDMA in the present case.

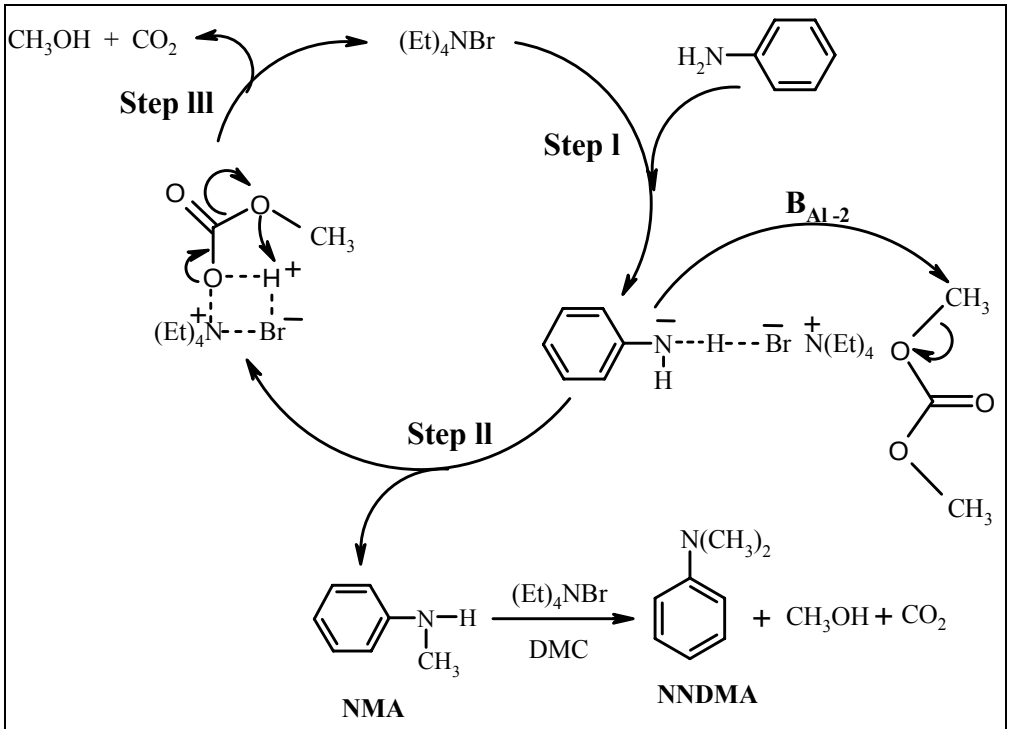
Table 3.5. *N*-alkylation of substrates showing networking of reaction scheme

Sr. No.	Substrate	Water	Alkylating agent	Conv. %	Product Yield, %			
					MPC	MMPC	NMA	NNDMA
1	MPC	No	DMC	90	0	90	0	0
2	MPC	Yes	DMC	50	0	0	0	50
3	NMA	No	DMC	100	0	18	0	82
4	NMA	Yes	DMC	100	0	0	0	99.8
5	Aniline	No	DMC	100	0	15	0	85
6	Aniline	Yes	DMC	100	0	0	0.2	99.8
7	Aniline	Yes	MeOH	0	0	0	0	0
8	MMPC	No	MeOH	0	0	0	0	0
9	MMPC	No	DMC	0	0	0	0	0

Reaction conditions: substrate, 16.1 mmol; alkylating agent, 190 mmol; TEAB catalyst, 3.57 mmol; H_2O, 111 mmol; T., 443 K; N_2 pressure, 3.4 MPa; Time, 2 h, Agitation speed, 13 Hz; Yields were determined by GC and are based on substrate conversion.

3.3.1.9. Plausible reaction mechanism

It is well known that ammonium quaternary salt would react with amine having active hydrogen to form a complex[17,20] ($R_4N^+ \ ^-X\cdots H\cdots NHAr$, Scheme 3.3, step I) containing nucleophilic anion ($PhHN^-$). This aniline nucleophile reacts with dimethyl carbonate through $B_{Al\text{-}2}$ mechanism (in which, nucleophile prefers to attacks on alkyl group when an acyl carbon is also available by SN_2 process) to generate *N*-methyl aniline (step II) and recovers back ammonium quaternary salt (step III). *N*-methyl aniline further undergoes *N*-alkylation reaction by DMC through similar catalytic cycle to give *N*,*N*-dimethyl aniline.



Scheme 3.3: Plausible catalytic cycle for N-alkylation of aniline

3.3.2. SYNTHESIS OF *N,N*-DIALKYL ANILINES USING IMMOBILIZED QUATERNARY SALT AND IMMOBILIZED IONIC LIQUIDS

Immobilized ionic liquids and quaternary salts are active catalyst for various types of reactions like: alkylation,[23] Friedel-Craft acylations[24] and C, O-alkylation[25] and nucleophilic substitution[26] respectively. In the present chapter, *N,N*-dialkylation of aromatic amines by dialkyl carbonate using immobilized ionic liquids and quaternary salts was demonstrated. These immobilized catalysts have the advantages of facilitating the separation of the catalyst from products, leading to uncontaminated product, can be recycled several times and can be used in gas phase reactions. In quest to overcome the separation of homogeneous catalyst like onium salts which involves energy intensive steps, immobilized catalysts were examined for the purpose of studying the efficiency of onium salts in heterogeneous form. Immobilized catalysts were synthesized as per reported procedure and used for the *N,N*-dimethylation reaction for the first time. Various aspects such as catalyst loading, reactivity of different aromatic amines and dialkyl carbonates and catalyst recycle have been studied.

3.3.2.1. Synthesis of immobilized catalysts

3.3.2.1.1. Synthesis of ionic liquids immobilized on silica gel

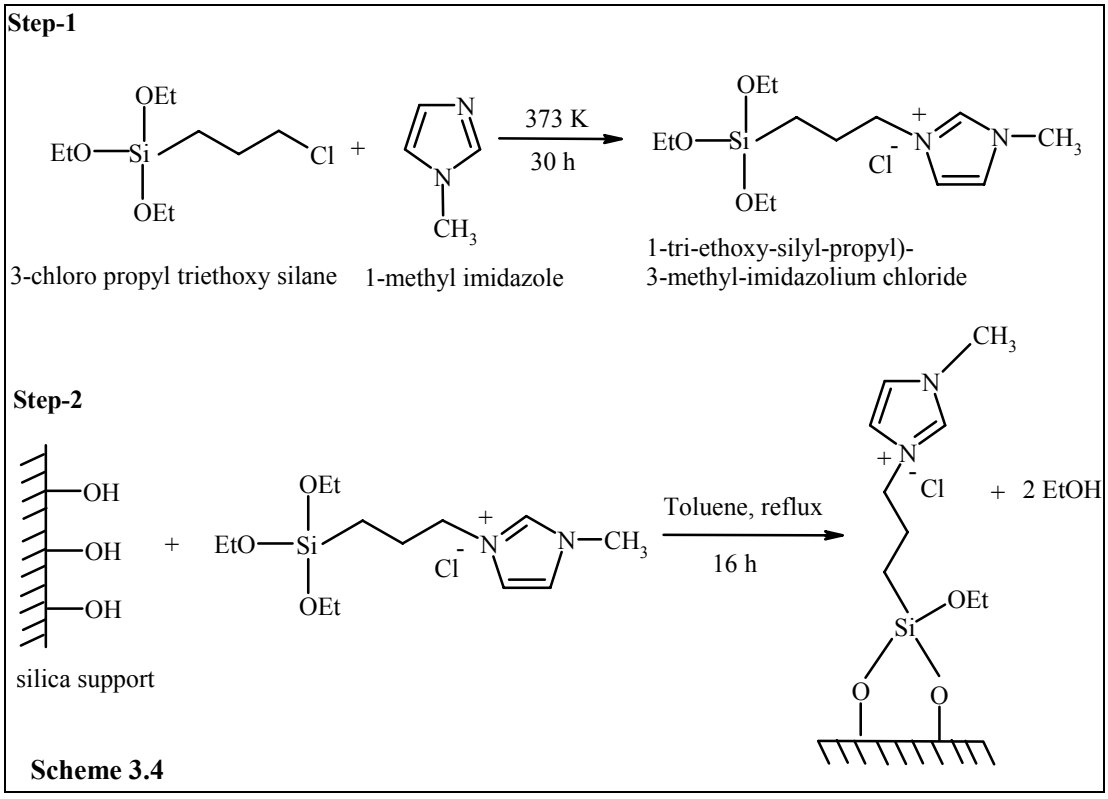
Following immobilized ionic liquids were synthesized as per literature procedure in two steps (Scheme 3.4).[27]

3.3.2.1.1.1. Synthesis of immobilized 1-(tri-ethoxy-silyl-propyl)-3-methyl- imidazolium chloride on silica support

Step 1- Synthesis of 1-(tri-ethoxy-silyl-propyl)-3-methyl-imidazolium chloride

In a round bottom flask equipped with a reflux condenser, a mixture of 1-methyl imidazole (20.53 g, 250 mmol) and 3-chloropropyl-tri-ethoxy-silane (60.2 g, 250 mmol)

were stirred at 383 K for 30 hrs under argon atmosphere. After completion of the reaction, the dense yellowish product was extracted several times with diethyl ether and dried under high vacuum at room temperature.



Scheme 3.4

Step 2- Immobilization of 1-(tri-ethoxy-silyl-propyl)-3-methyl-imidazolium chloride on silica support

Chromatographic grade Silica gel (Spectrochem, India, 200-400 mesh, pore diameter 60 Å, surface area ~ 400 m^2/g) was dried under reduced pressure (10^{-2} torr) at 773 K for 3 h. This dried silica (6 g) was dispersed in anhydrous toluene in a distillation apparatus. In that mixture, 1-(tri-ethoxy-silyl-propyl)-3-methyl-imidazolium chloride (3.23 g) was added and stirred at reflux temperature for 16h. The toluene and ethanol formed during grafting step were distilled off, solid catalyst was dried under high vacuum. Solid material was then subjected to Soxhlet extraction in boiling

dichloromethane so as to remove unreacted 1-(tri-ethoxy-silyl-propyl)-3-methyl-imidazolium chloride. After Soxhelt extraction treatment, solid material (**Cat-1**) was dried under reduced pressure (10^{-2} torr). Cat-1 contains 35 wt% immobilized ionic liquid and was well characterized by elemental analysis, DRIFT IR and ^{29}Si MAS NMR Spectroscopic technique.

The ^{29}Si MAS NMR Spectra of pure silica showed that a signal at -102.8 ppm corresponds to $(SiO)_3Si–OH$ group (Figure 3.7). While incase of Cat-1 (Figure 3.8), the peaks appeared at -59.7 and -68.9 were assigned for $Si–O–SiR–(OEt)_2$ and $(Si–O)_2–SiR–OEt$ repectively.[27,29] This showed that grafting of the organic cation on to the silica surface had successfully taken place. The organic cations were bonded to the surface either via one or two Si–O–Si bonds. The DRIFT IR (Figure 3.9) showed bands at 3105 and 3157 cm^{-1} confirmed the presence characteristic interaction of stretching frequency resulting from H-bonding interaction of C_4/C_5 hydrogen with Cl^- and C_2 hydrogen with Cl^- respectively.[28] The band between 1350-1482 cm^{-1} are attributed to CH_3-C-H asymmetric stretching vibrations of imidazole ring.

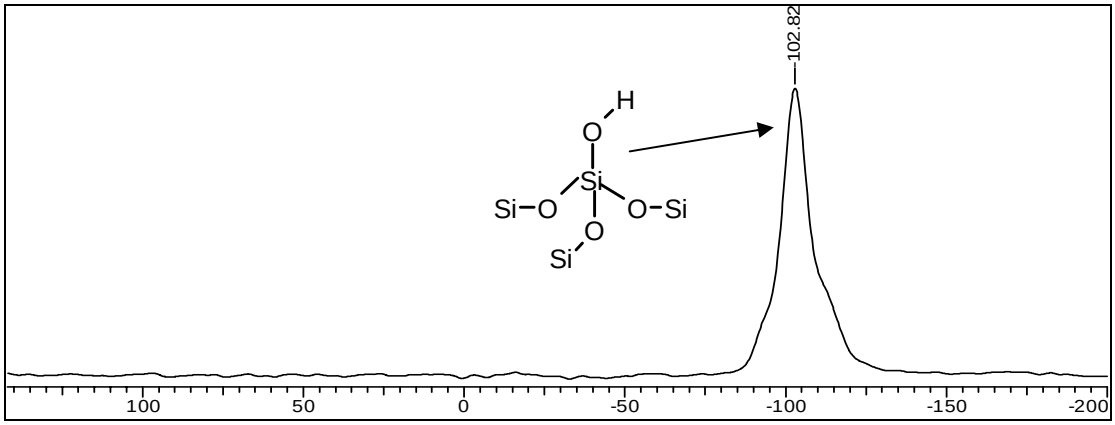


Figure 3.7. ^{29}Si MAS NMR Spectra of pure SiO_2

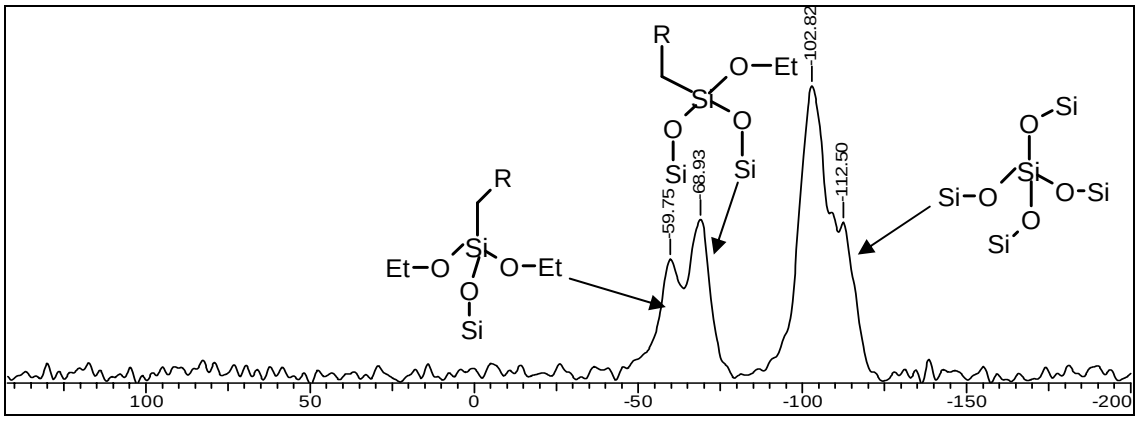


Figure 3.8. ^{29}Si MAS NMR Spectra of $(EtO)_3$-Si-propyl-imidazolium chloride immobilized on SiO_2

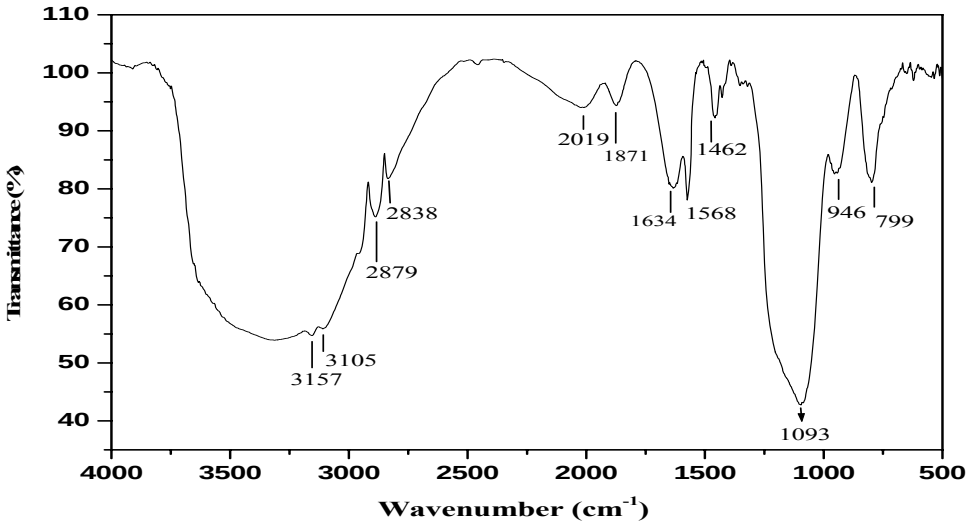


Figure 3.9. DRIFT IR Spectra of $(EtO)_3$-Si-propyl-imidazolium chloride immobilized on SiO_2

3.3.2.1.1.2. Synthesis of immobilized 1-(tri-ethoxy-silyl-propyl)-pyridinium chloride on silica support

1-(tri-ethoxy-silyl-propyl)-pyridinium chloride immobilized on silica (Cat-2) was synthesized by replacing cationic part (1-methyl imidazole) by pyridine following the above mentioned procedure. Cat-2 contains 35 wt% immobilized ionic liquid and was characterized by elemental analysis, ^{29}Si MAS NMR Spectroscopic technique (Figure 3.10) and DRIFT IR (Figure 3.11).

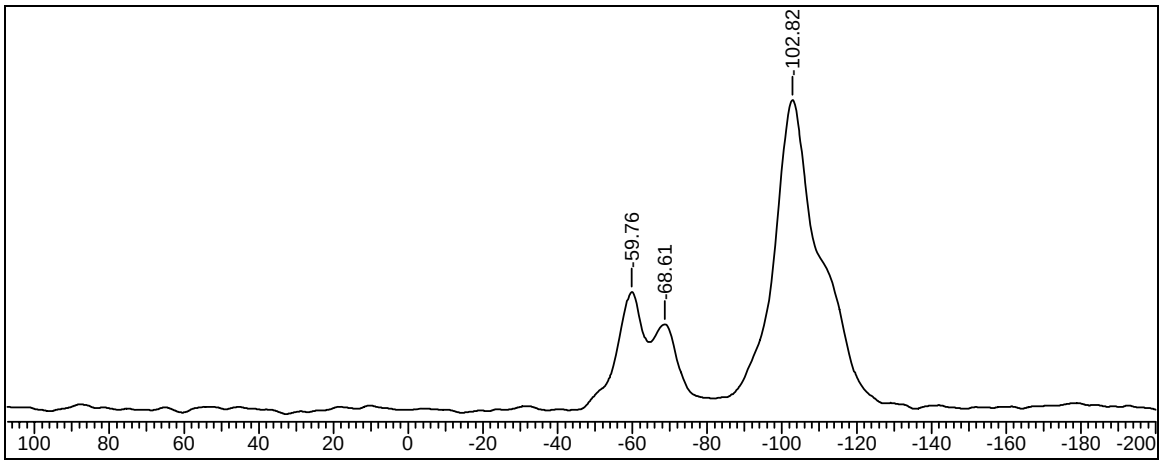


Figure 3.10. ^{29}Si MAS NMR Spectra of $(EtO)_3$-Si-propyl- pyridinium chloride immobilized on SiO_2

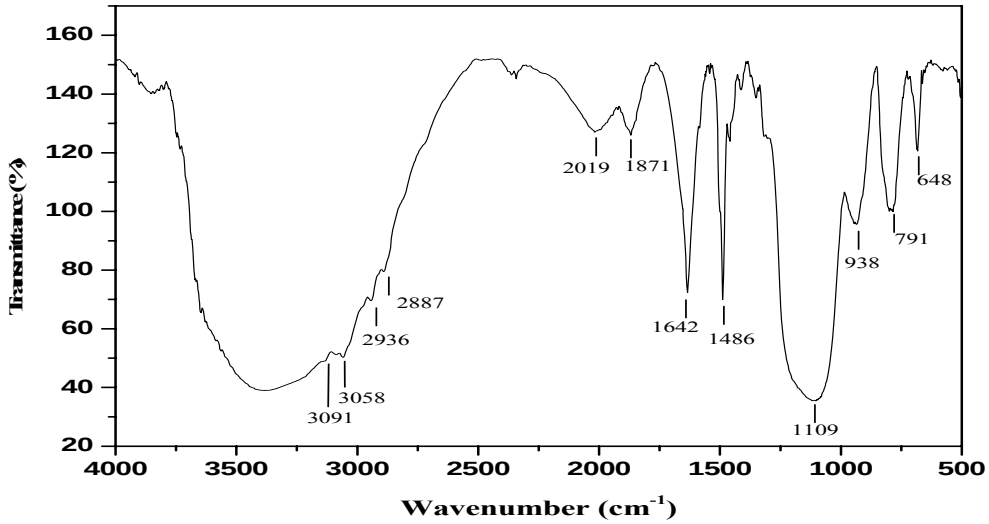


Figure 3.11. DRIFT IR Spectra of $(EtO)_3$-Si-propyl-pyridinium chloride immobilized on SiO_2

3.3.2.1.2. Synthesis of quaternary salt immobilized on silica gel[25]

Immobilized quaternary salt was synthesized in two steps (Scheme 3.5).

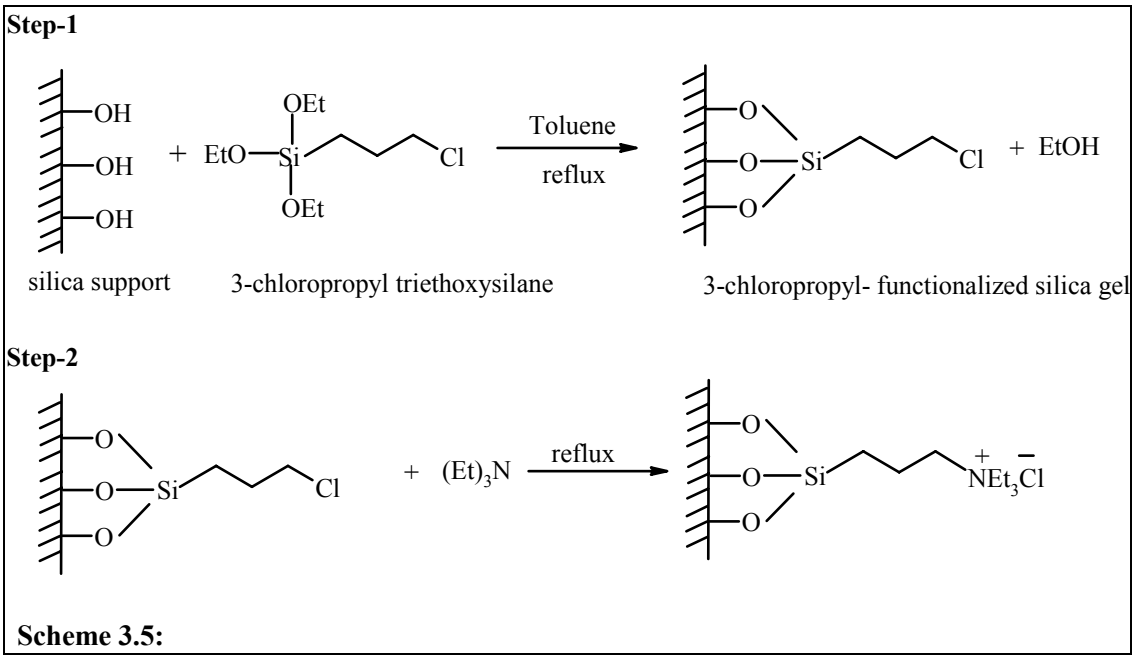
Step1- Synthesis of 3-chloropropyl-functionalized silica gel

In a 250 ml round bottom flask equipped with a reflux condenser, a suspension of 3-chloropropyltriethoxysilane (3.63 g, 15 mmol) and activated silica gel[30] (10g, activated

by refluxing it in conc. HCl for 4h), in 100 ml anhydrous toluene was refluxed with stirring. After 3 h, toluene containing ethanol about 25 ml was removed by distillation and reflux was continued. Again after 2h, 25 ml ethanol-containing toluene was removed and reflux was continued for 2 h. The reaction mass was cooled at room temperature and functionalized silica gel was filtered, washed several times with diethyl ether and allowed it to dry at room temperature. Yield of functionalized silica gel was 11.5 g.

Step2- Synthesis of immobilized quaternary ammonium salt

The 3-chloropropyl-functionalized silica gel (5 g) in 25 ml tri-ethyl amine was degassed under vacuum and refluxed at 361 K without stirring for 5 days. After cooling, the reaction mass was filtered washed several times with diethyl ether and dried at room temperature. Yield of immobilized ammonium quaternary salt (35 wt%, Cat-3) was 7.68 g and characterized by elemental analysis and DRIFT IR spectroscopy (Figure 3.12).



Scheme 3.5:

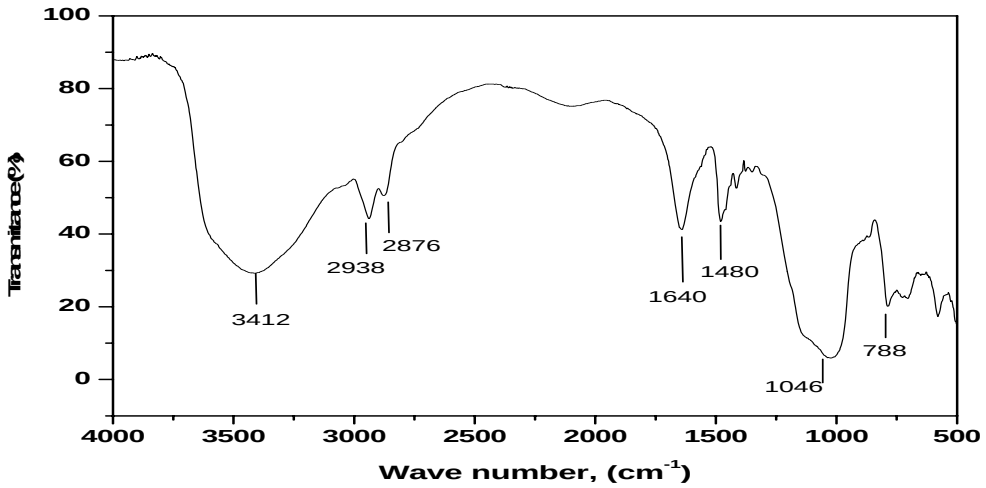
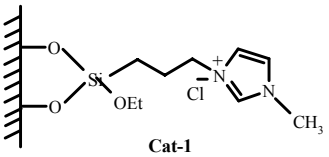
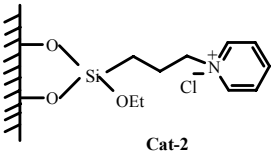
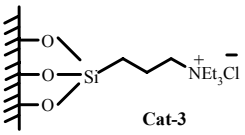


Figure 3.12. DRIFT IR Spectra of immobilized quaternary ammonium salt on SiO_2

Details of immobilized catalyst characterizations are presented in the Table 3.6.

Table 3.6. Characterization data of immobilized catalysts

Catalyst (~35 wt% loading)	Surface area, m^2/g	C, H, N analysis	Drift IR in KBr, cm^{-1}	^{29}Si MAS NMR, δ
 Cat-1	89	C, 11.05%; H, 2.0%; N, 3.56%	3157, 3105, 2879, 2838, 1871, 1568, 1462, 1093, 946, 799	-59.75, -68.93, -102.82, -112.5
 Cat-2	69	C, 13.15%; H, 2.96%; N, 2%	3091, 3058, 2936, 2887, 1871, 1486, 1443, 1109, 938, 791	-59.76, -68.61 -102.82
 Cat-3	102	C, 14.2%; H, 2.5%; N, 2.01%	2938, 2876, 1480, 1416, 1076, 788, 732	-

3.2.2.2. Activity of immobilized catalyst towards *N*-alkylation reaction

Following the same experimental procedure described in Section 3.2.2, various immobilized catalysts were screened for the *N*-alkylation reaction of aniline and DMC in

absence of water (Table 3.7). From the catalyst screening it was observed that catalysts like: Tixogel-VP (quaternary ammonium compound of bentonite, obtained from süd chemie, Germany), Cat-2 and Cat-3 gave lower yield of NNDMA (entry 2, 4 and 5) while, Cat-1 gave better yield of NNDMA (62%, entry 3). It was also observed that Cat-1 in comparison to the pure ionic liquid (C_4MIMCl) gave more yield of *N*-alkylated products while, C_4MIMCl gave carboxylated compounds (carbamate) as major products (entry 1). Hence, further *N*-alkylation reactions of various aromatic amines and dialkyl carbonates were carried out using Cat-1 as catalyst.

Table 3.7. Screening of catalyst

Entry	Catalyst	Aniline conversion, %	NMA yield, %	NNDMA yield, %	MMPC yield, %	MPC yield, %
1	C_4MIM-Cl	97.5	3.4	31.9	51.6	10.5
2	Tixogel-VP	37.1	15.4	4.5	16	1.2
3	Cat-1	95.5	9.4	61.8	20.6	3.6
4	Cat-2	47.5	23.8	8.5	0.6	14.7
5	Cat-3	78.6	38.6	15.4	3.1	21.5

Reaction conditions: aniline, 5.4 mmol; dimethyl carbonate, 215 mmol; solid catalyst, 2 g (C_4MIM-Cl, 3.5 mmol); T., 443 K; P_{N2}, 3.4 MPa; Time, 4 h; Agitation speed, 13 Hz; reaction volume, 20 ml; [a] yields were determined by GC and are based on aniline conversion

Reaction of aniline and dimethyl carbonate in presence of Cat-1 gave 70% *N*-alkylated products (NMA + NNDMA) and 25% carboxylated products (MMPC + MPC, Table 3.7, entry 3). From the previous study, it was known that *N*-alkylation of anilines by DMC in presence of water using TEAB catalyst gave high yields of *N,N*-dimethylated anilines (> 99%). Therefore, same experimental procedure was followed for Cat-1 (Section 3.2.2.). It was observed that reaction of aniline with DMC in presence of water at 443 K gave 32% yield of NMA and 30.4% yield of NNDMA in 4 h without any

formation of carboxylated products (Table 3.8, entry 1). Whereas, high selectivity and yield of NNDMA (> 98%) was achieved by carrying out the reaction for longer run time (Table 3.8, entry 2).

3.3.2.3. Effect of catalyst loading

Effect of catalyst loading on the conversion and selectivity of NMA and NNDMA is shown in Figure 3.13. From the plot, it can be seen that both conversion of aniline and yields of *N*-alkylated products increased with increase in Cat-1 loading. NNDMA was formed via an intermediate NMA and thus catalyst was involved in both steps and hence did not show expected linear dependency of aniline conversion with catalyst loading.

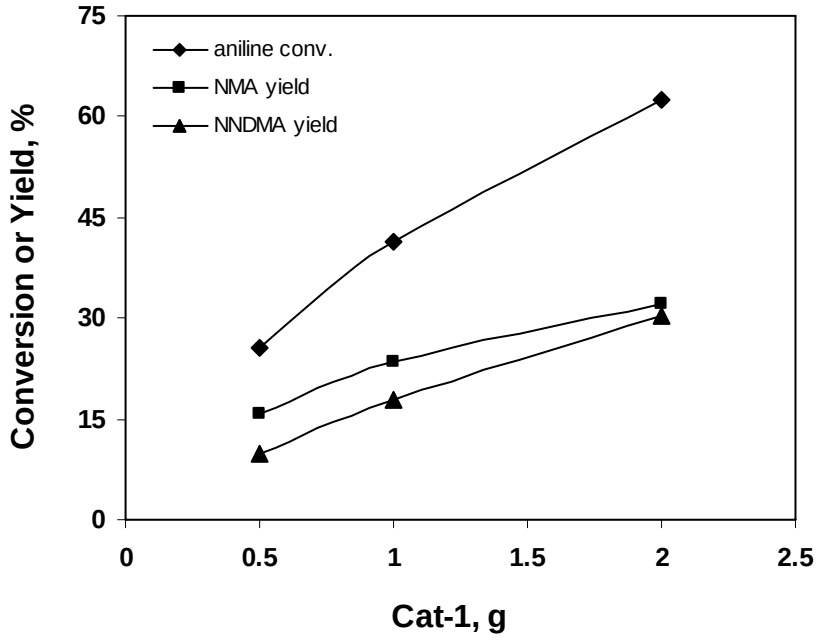


Figure 3.13. Effect of Cat-1 catalyst loading on NNDMA yield

<u>Reaction conditions</u>: aniline, 5.4 mmol; DMC, 215 mmol; H_2O, 55 mmol; T., 443 K; N_2 pressure, 3.4 MPa; Time, 4 h, Agitation speed, 13 Hz; Total volume, 20 ml; Yields were determined by GC and are based on aniline conversion.

3.3.2.4. Effect of Substrate

Various aromatic amines were screened to examine the wide applicability of the Cat-1 catalyst and to study the reactivity of the substrates toward *N*,*N*-dimethylation reaction. The results are summarized in Table 3.8. In most of the cases, *N*,*N*-dimethylated products were obtained with excellent selectivity and yields (> 95%) except *o*-chloro aniline and *p*-nitro aniline. Aromatic amines showed the similar reactivity pattern, which was observed for TEAB catalyst for *N*,*N*–dimethylation reaction. The presence of electron-donating groups (-CH_3, -OCH_3) on the benzene ring would increase the activity of amines that increases the yield of *N*,*N*- dimethylated products (see entry 3, 4). While, electron-withdrawing groups (-Cl, -NO_2) on the benzene ring would decrease the activity of amines and yields of *N, N*- dimethylated products (entry 7, 8).

Activity of various dialkyl carbonates has been also examined for aniline alkylation reaction. It was observed that activity of carbonates as alkylating agent decreased in order of DMC > DEC > DBC in accordance with increase in steric hindrance from DMC to DBC. High yield of *N*,*N*- dialkylated product was obtained in case of DMC. Negligible yield of *N*,*N*- dialkylated product was obtained from DEC while, DBC was inefficient for *N*,*N*- dialkylation reaction (entry 9, 10).

Table 3.8. Synthesis of *N,N*- dialkyl anilines using Cat-1 catalyst

Entry	Amine	Amine conversion, %	Dialkyl yield[a] %	Mono alkyl yield[a], %	Other products[b] yield[a], %
1[c]	$C_6H_5NH_2$	62.4	30.4	32	0
2	$C_6H_5NH_2$	99.7	98.3	1.4	0
3	4-CH_3-$C_6H_4NH_2$	99.8	97.8	1.9	0.1
4	4-OCH_3-$C_6H_4NH_2$	99.5	97.8	1.7	0
5	4-Cl-$C_6H_4NH_2$	99.2	96.7	2.0	0.5
6	3-Cl-$C_6H_4NH_2$	98.7	96	2.1	0.6
7	2-Cl-$C_6H_4NH_2$	52.2	7.7	43.9	0.6
8	4-NO_2-$C_6H_4NH_2$	44.2	13.8	25.5	4.9
9[d]	$C_6H_5NH_2$	15.7	2.8	11.9	1
10[e]	$C_6H_5NH_2$	8.9	0	8.9	0

Reaction conditions: amine, 5.4 mmol; DMC, 215 mmol; Cat-1 catalyst, 2 g; H_2O, 55 mmol; T., 443 K; N_2 pressure, 3.4 MPa; Time, 12 h; Agitation speed, 13 Hz; reaction volume, 20 ml; [a] yields were determined by GC and are based on aniline conversion; [b] N-carbamtes; [c] reaction time, 4h; [d] diethyl carbonate; [e] dibutyl carbonate

3.3.2.5. Catalyst recycles study

The most important feature of heterogeneous catalyst is its reusability. Therefore, reusability of Cat-1 was studied for the reaction of aniline with DMC in presence of water and the results are shown in Figure 3.14. Catalyst was separated from the reaction mixture by simple filtration and washed several times with acetonitrile to remove any adhered organic impurities and then dried at 373 K. This recovered catalyst was used for new reaction. The recycle study showed the excellent reusability of Cat-1 catalyst without any loss in its catalytic activity.

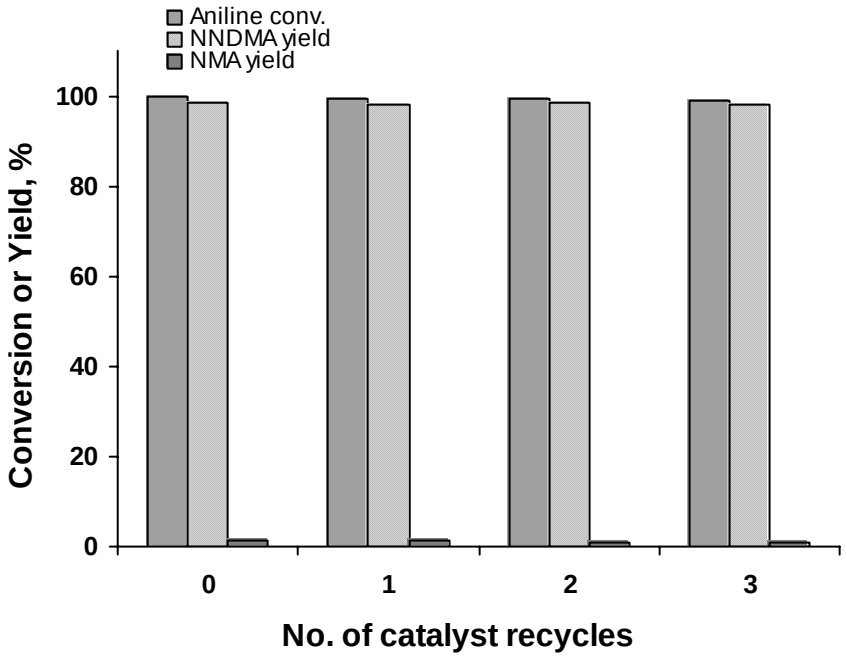


Figure 3.14. Cat-1 catalyst recycles study

Reaction conditions: aniline, 5.4 mmol; DMC, 215 mmol; Cat-1 catalyst, 2 g; H_2O, 55 mmol; T., 443 K; N_2 pressure, 3.4 MPa; Time,12 h, Agitation speed, 13 Hz; Total volume, 20 ml; Yields were determined by GC and are based on aniline conversion.

3.4. CONCLUSION

Selective *N*,*N*-dimethylation of aromatic amines with dimethyl carbonate in presence of water using simple and efficient catalysts consisting of onium salts and immobilized ionic liquid was demonstrated for the first time. It was observed that activity of immobilized ionic liquid, Cat-1 (TOF; 0.2 $^{-1}$h) was almost ten times less than homogeneous TEAB catalyst (TOF; 2.25 $^{-1}$h). Water plays an important role in increasing the selectivity of *N*,*N*-dialkylated products (~99%) by hydrolyzing the side product such as carbamates to amines. Reactivity study of aromatic amines and organic carbonate was investigated and it was observed that excellent yield of dialkyl products

were obtained in case of aromatic amines having electron donating substituents on their ring and low yields for electron withdrawing substituents on ring. The activity of dialkyl carbonates as alkylating agents towards aniline was found to decrease in the order of dimethyl carbonate > diethyl carbonate > dibutyl carbonate as steric hindrance increases from dimethyl carbonate to dibutyl carbonate. The catalyst recycle experiments showed that there was no loss in catalytic activity for both catalysts (TEAB and Cat-1) even after several recycles. Even though, both the catalysts showed good recyclability, homogeneous TEAB catalyst suffered from energy intensive recovery procedures.

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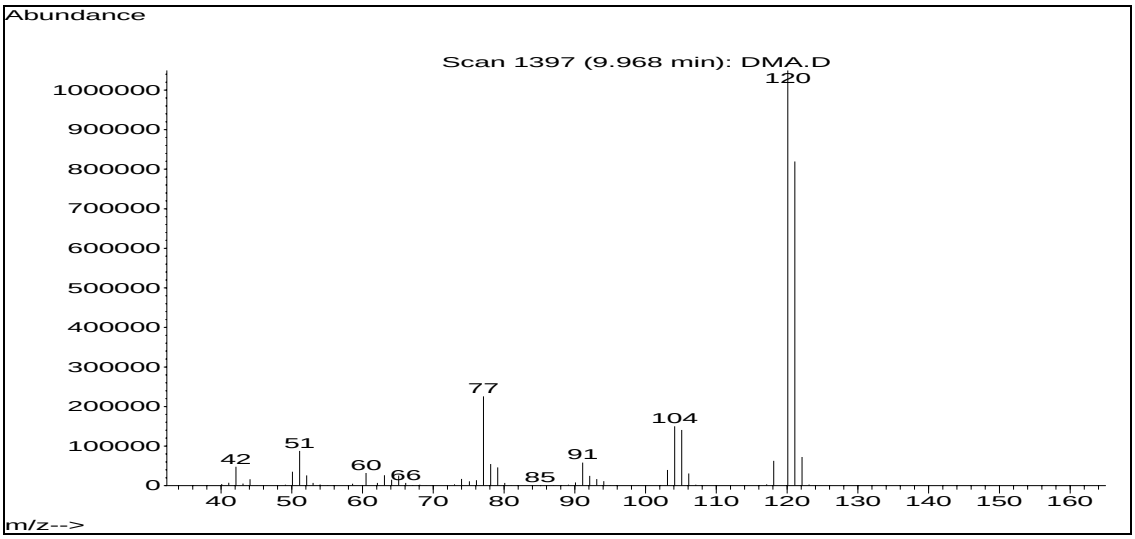
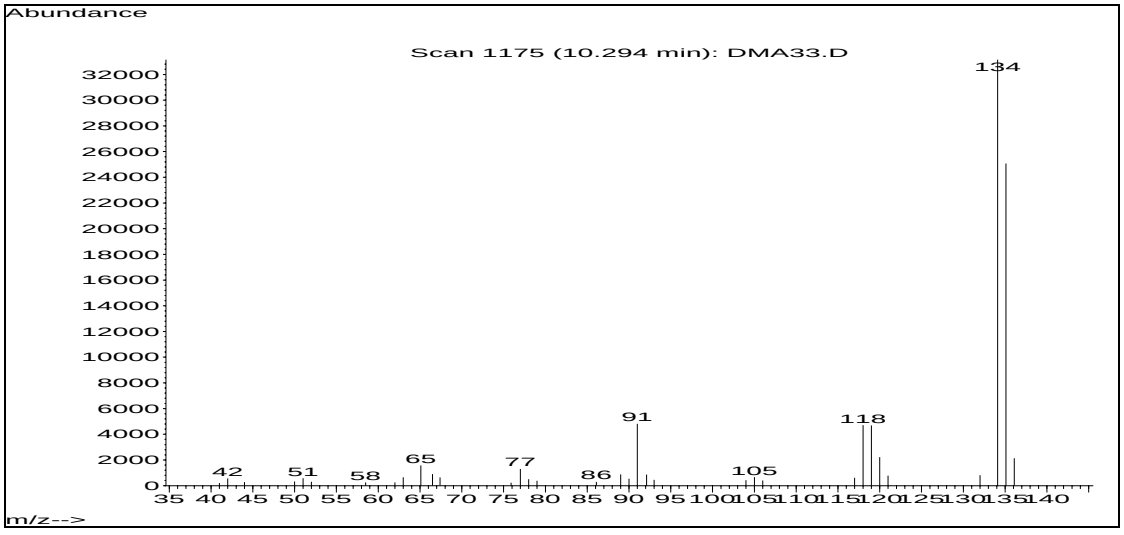
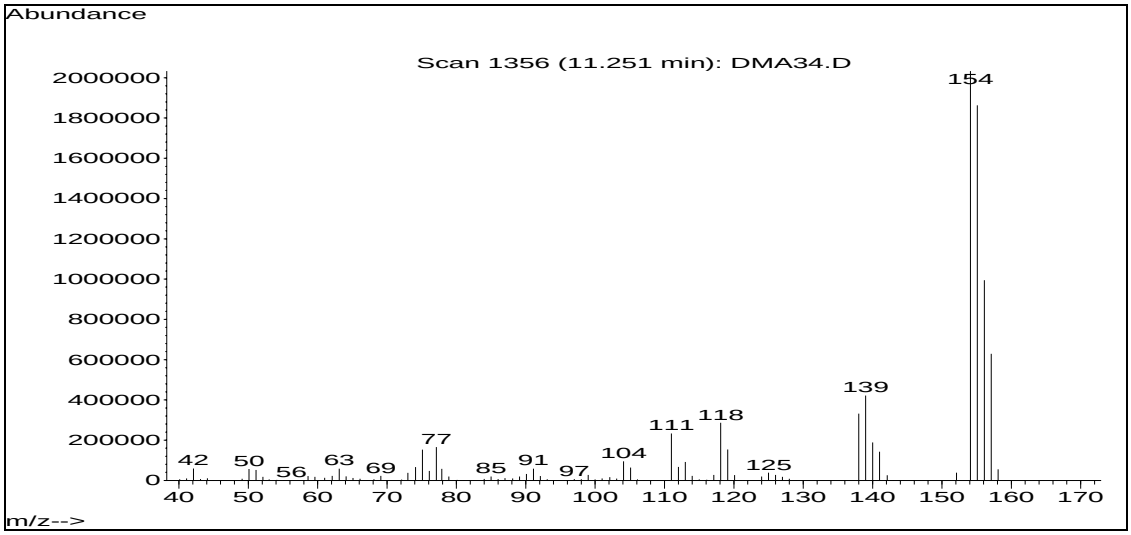
SPECTRA



GC-MS Spectrum of *N*,*N*-dimethyl aniline (70 eV, EI)



GC-MS Spectrum of compound *N*,*N*-dimethyl *p*-toluidine (70 eV, EI)



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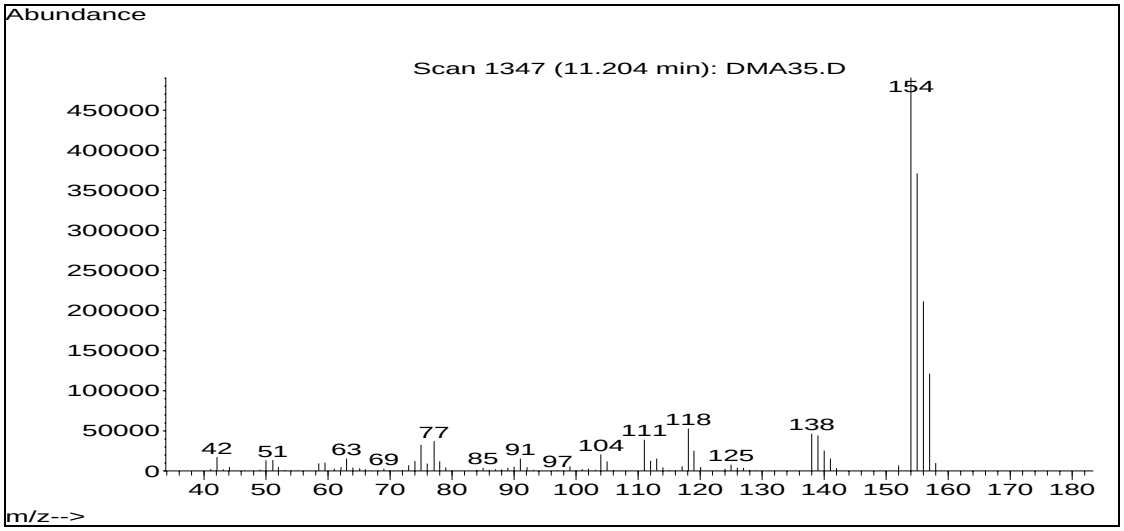
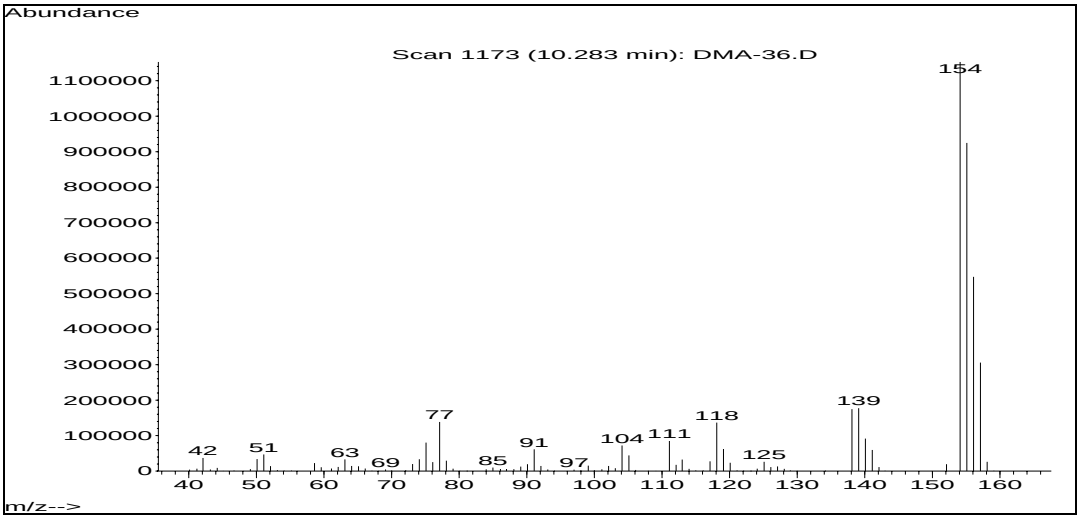
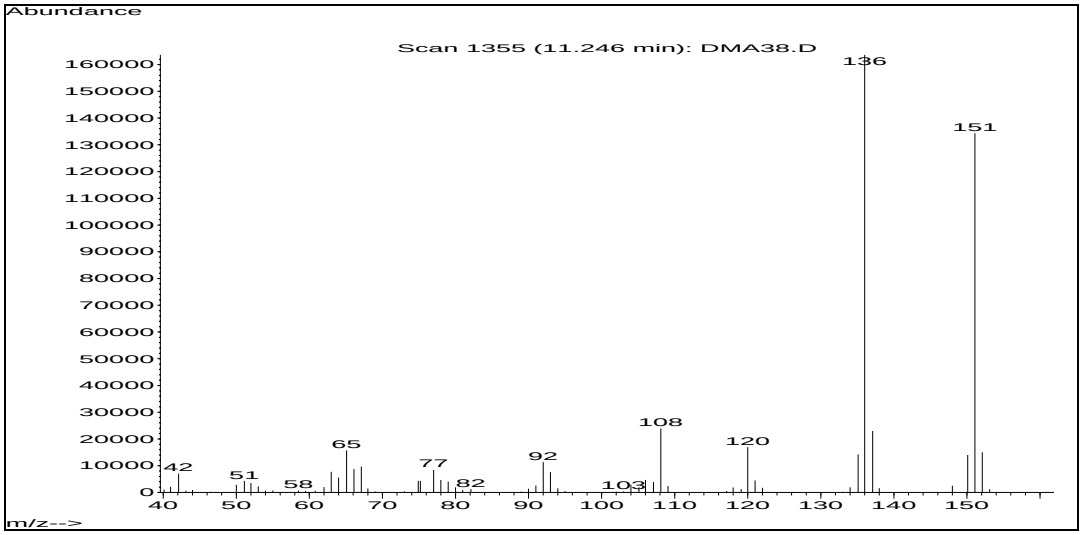


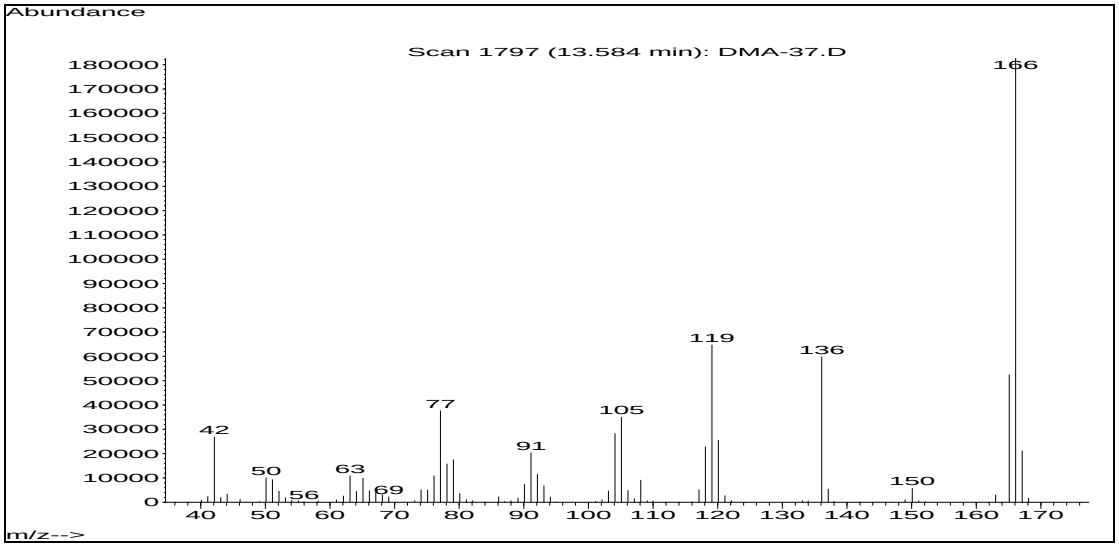
GC-MS Spectrum of compound *N*,*N*-dimethyl *m*-chloroaniline (70 eV, EI)



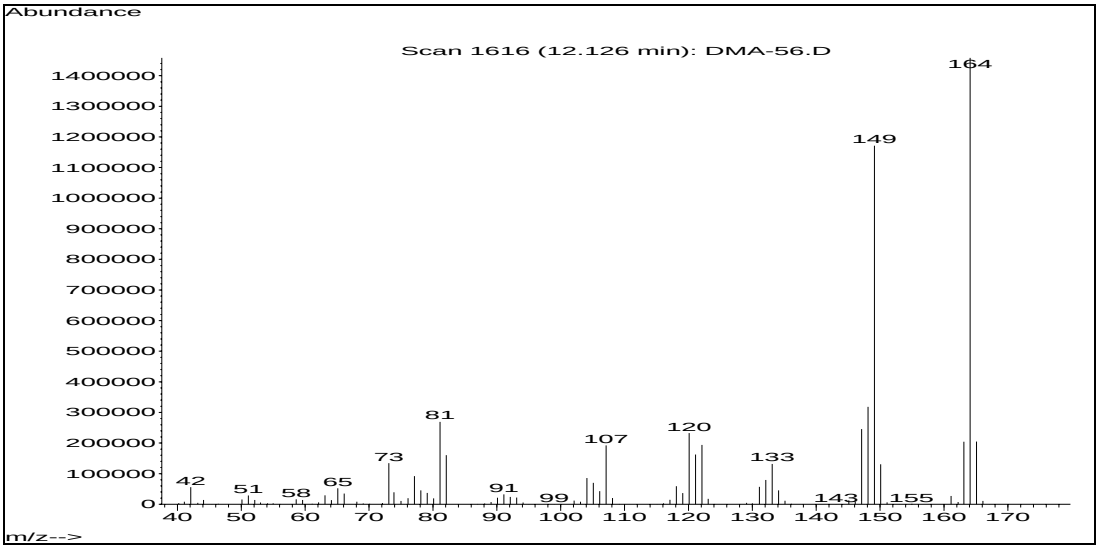
GC-MS Spectrum of compound *N*,*N*-dimethyl *o*-chloroaniline (70 eV, EI)



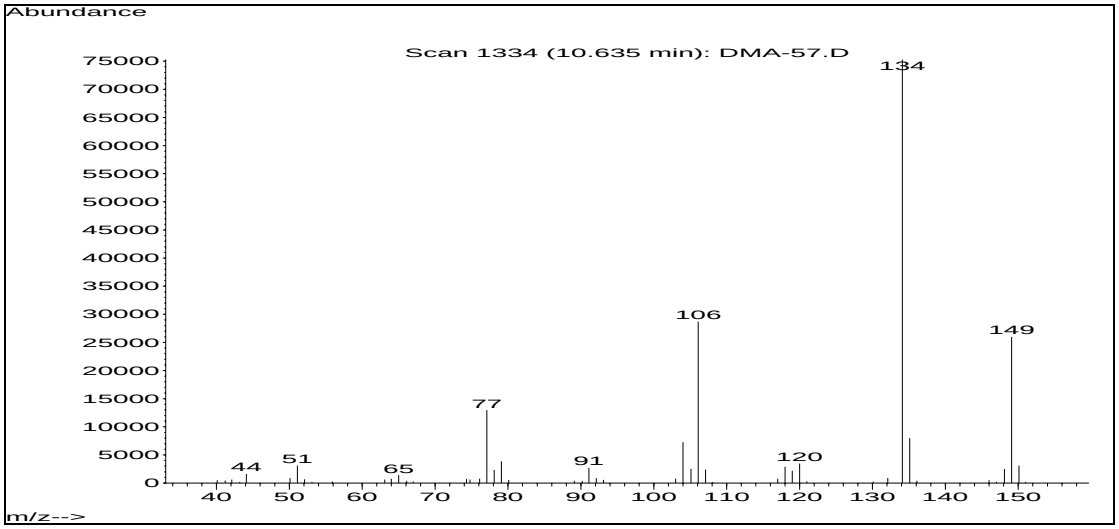
GC-MS Spectrum of compound *N*,*N*-dimethyl *p*-anisidine (70 eV, EI)



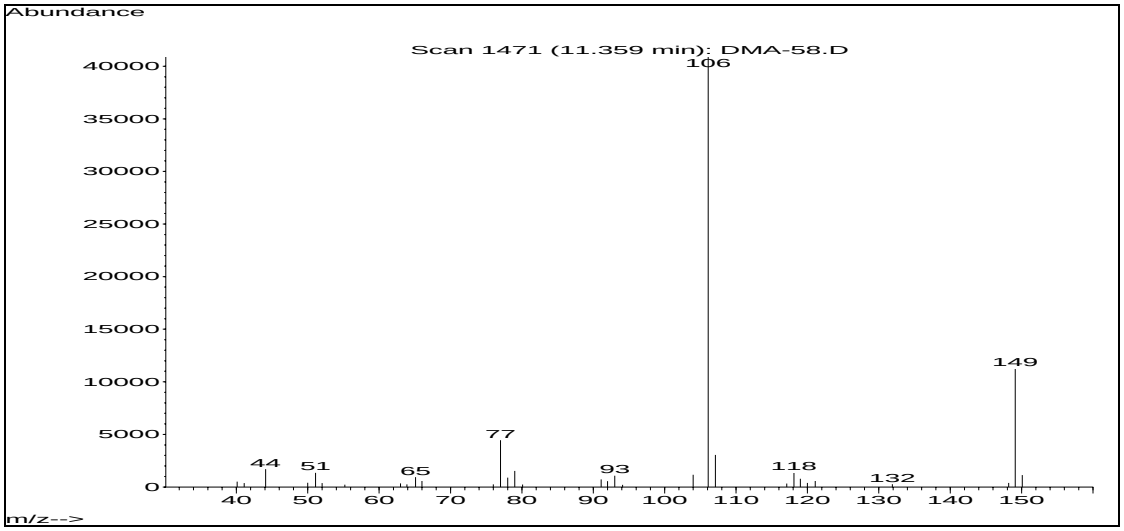
GC-MS Spectrum of compound *N*,*N*-dimethyl *p*-nitrroaniline (70 eV, EI)



GC-MS Spectrum of compound *N*,*N*,*N*',*N*'-tetramethyl 1,4 phenylenediamine (70 eV, EI)



GC-MS Spectrum of compound *N*,*N*- diethyl aniline (70 eV, EI)



GC-MS Spectrum of compound *N*- butyl aniline (70 eV, EI)

Chapter 4

Synthesis of β-amino alcohols from Aromatic amines and Alkylene Carbonate

4.1. INTRODUCTION

β-amino alcohols are an important class of organic compounds due to their high occurrence in nature and their use as versatile intermediates in the synthesis of pharmaceuticals and biological active natural products, synthetic amino acids and chiral auxiliaries for asymmetric synthesis.[1] They are also useful as intermediates in the synthesis of perfumes,[2] dyes,[3] photo developers[3] and oxazolidones.[4]

Conventionally β-amino alcohols are produced from the nucleophilic ring opening of epoxides with an excess of amines at elevated temperature.[3,5] This classical approach, involving heating of alkylene oxides with amines works less well with poorly nucleophilic amines such as anilines. Hence, various methodologies are developed to overcome this problem include the use of variety of activators and promoters such as metal triflates,[6] metal halides,[7] metal amides,[8] alkali metal perchlorates,[9] clays,[10] silica[11] and ionic liquids.[12] However these routes suffer from the draw back of handling of hazardous alkylene oxides, stoichiometric amount of reagents, longer reaction time, high pressure and temperature conditions.

Whereas, synthesis of β-amino alcohols using alkylene carbonates is attractive due non-hazardous nature of alkylene carbonate.[13] Alkylene carbonates are easy to handle and do not require high pressure reaction setup often necessary when working with highly volatile epoxides (especially when working with ethylene oxide).

N-alkylation[14] and alkoxy carbonylation[15] of amines by dimethyl carbonate to *N*-alkyl amine and carbamate respectively is known in the literature. However, the extension of this methodology to the preparation of β-amino alcohols is not well investigated.[13] Gulbins and Hamann reported the reaction of aromatic amines with

alkylene carbonate in the presence of LiCl as a catalyst to give oxazolidones as the major products, along with β-amino alcohols.[16] Kaye et al.[17] reported the synthesis of *N*-methyl *N*-phenyl ethanolamine from *N*-methyl aniline and ethylene carbonate using corrosive and flammable homogeneous lithium amide catalyst. It was also reported that reaction between amine and alkylene carbonate gives polymeric products having carbamate and carbonate functionality.[18] Patented literature on this reaction revealed that the use of solid base catalysts such as mixed metal oxides and hydrotalcite could be effective.[19] However, these catalysts showed poor activity and were not attractive from synthetic viewpoint. Thus, there is a scope to develop an efficient method for β-amino alcohol synthesis since; there is no detailed information in the literature on this simple but useful reaction.

In view of this, objective of the present work was to develop new catalytic system as well as route for the synthesis of β-amino alcohol. In this chapter, experimental results on *N*-alkylation of aromatic amines by alkylene carbonate to β-amino alcohols are presented using Na-Y zeolite catalyst system. Effect of various parameters, reactivity of aromatic amine and alkylene carbonate, and catalyst recycles have been studied. In this work, tandem synthesis of β-amino alcohols from aniline, dialkyl carbonate and ethylene glycol using Na-Y zeolite catalyst was also demonstrated for the first time. In this synthesis, ethylene carbonate is generated in-situ by transesterification reaction of dialkyl carbonate and ethylene glycol which reacts further with aniline to give β-amino alcohol. Various process parameters such as substrate concentration, Na-Y catalyst loading and temperature effect on conversion of aniline and selectivity of β-amino alcohol have been studied. Synthesized β-amino alcohols were characterized by IR, NMR and GC-MS analysis.

4.2. SYNTHESIS OF β-AMINO ALCOHOLS FROM AROMATIC AMINES AND ALKYLENE CARBONATE

4.2.1. EXPERIMENTAL SECTION

4.2.1.1. Materials

Cyclohexyl amine, benzyl amine, aniline, various substituted aromatic amines, dimethyl carbonate (DMC), diethyl carbonate (DEC), ethylene glycol (EG), ZnO, MgO, $PbCO_3$, were purchased from M/s S. D. fine chemicals, India. Ethylene carbonate, propylene carbonate, (R or S) propylene carbonate (98% ee), tri-ethylene glycol dimethyl ether (triglyme), n-dibutyl tin oxide (DBTO), tetraethyl ammonium bromide (TEAB), PbO, $PbZrCO_3$ and Cs_2CO_3 were purchased from Aldrich chemicals, USA. Faujasites Na-Y and Na-X were obtained from Süd-Chemie, India and Laporte-inorganic UK, respectively and were characterized by XRD analysis (see Section on Spectra, page no. 226). Amines were freshly distilled or recrystallized prior to use.

4.2.1.2. General procedure for β-amino alcohol synthesis

In a typical experimental procedure, known quantities of amine, alkylene carbonate, catalyst and solvent (triglyme) were charged to a dried round bottom flask (50 ml) equipped with temperature controller, a stirrer and reflux condenser. The contents were flushed with nitrogen and heated to desired temperature into preheated oil bath. After the reaction, reaction mixture was cooled to room temperature, filtered to separate the catalyst and the liquid phase was quantitatively analyzed by GC.

Isolation of product: In the reaction crude, 15-20 ml water was added and then it was extracted with diethyl ether (3 × 20 ml). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The products were separated from concentrated

organic phase by flash chromatography on a 4 g normal phase silica RediSep column employing n-hexane-ethyl acetate as the eluent with gradient programming. Liquid chromatography was performed using CombiFlash Companion, supplied by Teledyne ISCO, USA. Products were characterized by GC-MS, IR, ^{1}H NMR and ^{13}C NMR spectroscopy. Spectral data of all synthesized β-amino alcohol is given in the section; Spectra.

4.2.1.3. Analytical methods

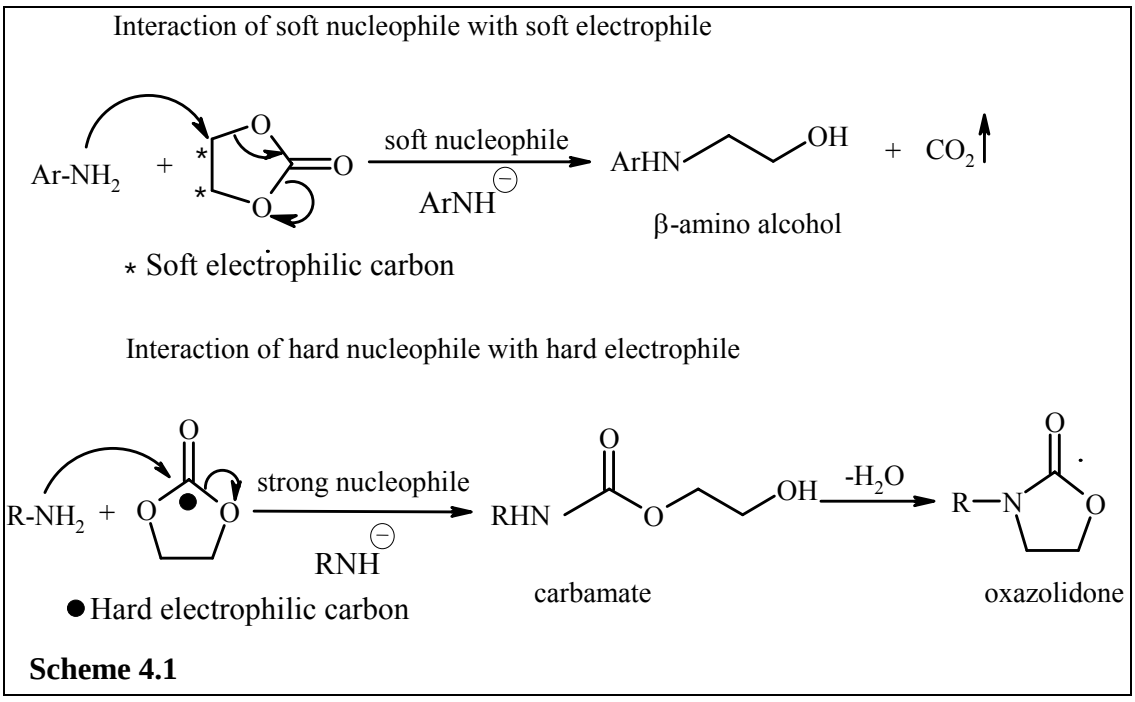
IR spectra were obtained using a Perkin Elmer Spectrum-2000 in transmission mode. NMR was obtained from a Brucker-Av-200 and Brucker-Av-400 machines. Shimadzu HPLC with UV detector (λ, 254 nm) containing Chiralcel® OD-H column was used for analysis of chiral amino alcohols. Liquid samples were analyzed on a Hewlett Packard 6890 Series GC equipped with auto sampler instrument, controlled by the HP Chemstation software, and using an HP-1 capillary column (30 m x 320 μm x 0.25 μm film thickness, on 1% phenyl methyl siloxane stationary phase). Mass spectrometry was performed on GC-MS (70eV, EI) instrument supplied by M/s. Agilent, USA, equipped with auto-sampler employing earlier standardized GC method. The standard conditions for GC analysis are given in Table 4.1

Table 4.1. Standard conditions for GC analysis

Parameters	Conditions
Injector (split) temperature	523 K
Flame ionization detector (FID) temperature	573 K
Column temperature (HP-1 capillary column)	343 K–563 K (programmed)
Inlet Pressure (He)	5 psig –10 psig (programmed)
Carrier gas (He) flow rate	0.8 ml/min
Split ratio	50:1

4.2.2. RESULTS AND DISCUSSION

The use of alkylene carbonates like ethylene carbonate (EC), propylene carbonate (PC) has risen dramatically in the past few years and has grown to encompass several additional areas of active research as they are biodegradable and have high boiling points, flash points, high solvency, low odour levels and toxicities. Alkylene carbonate has two types of electrophilic carbon, a hard carbonyl carbon (sp^2 carbon) and a soft methylene carbon (sp^3 carbon). The possibility of amine nucleophile attacking on both electrophilic carbons can be understood on the basis of HSAB theory.[20] And according to HSAB theory, aromatic amine being the softer nucleophile will preferably attack on soft electrophile methylene carbon producing β-amino alcohol.[21] While, aliphatic amines (hard nucleophile) attack on carbonyl carbon (hard electrophile) giving rise to carbamates (Scheme 4.1). These carbamates further undergo cyclization to give oxazolidones.[4]



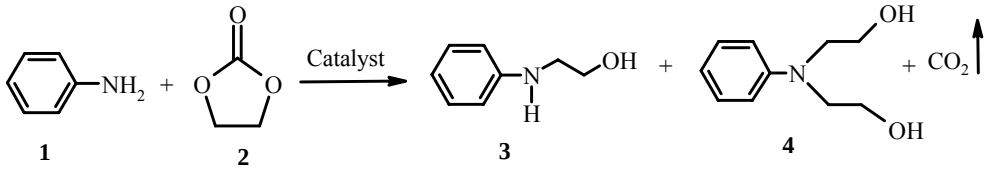
Scheme 4.1

4.2.2.1. Preliminary experiments for catalyst screening

Various homogeneous and heterogeneous catalysts were screened for the *N*-alkylation reaction of aniline and ethylene carbonate and results are presented in Table 4.2. It was observed that a non-catalytic reaction between aniline and ethylene carbonate gave less than 5% yield of *N*-phenyl ethanolamine (NPEA), indicating that the reaction was quite slow and had no practical utility in the absence of any catalyst (Table 4.2, entry1). Soluble catalyst, tetraethyl ammonium bromide (TEAB) was examined for the catalytic performance and it was found that NPEA was not formed selectively. Further *N*-alkylation of NPEA occurred to form appreciable quantity of *N*-phenyl diethanolamine, which decreased NPEA selectivity (entry 2). Several catalytic materials consisting of solid base catalysts such as metal oxides (MgO, PbO, ZnO,) and hydrotalcite reported earlier in the patented literature were examined for their performance.[19] Some other solid base catalysts like carbonates ($PbCO_3$, Cs_2CO_3, $PbZrCO_3$) were also tested for this reaction. It was clear from the results that these catalysts showed poor yields (2-18%) of β-amino alcohols indicating that they were inefficient from practical point of view (entry 3-9). Solid base zeolites were also examined and it was noticed that except, alkali cation exchanged zeolite X and Y, other zeolite-based materials viz. Na-ZSM5, KNO_3 on KL, 4A and H-Y showed very poor yields (up to 30%; entry 11-14). Since zeolite X and Y, showed a significant enhancement in yields (entry 15-16, yield >95%) over other catalysts for *N*-alkylation of aniline by ethylene carbonate and also due to their benign nature and excellent reusability further exploitation of the substrate effects were carried out using Na-Y zeolite as catalyst. Na-Y zeolite is usually considered as amphoteric in nature.[22] The basicity of Na-Y zeolite is due to the framework of AlO_4^-, the excess

negative charge of which is compensated by Na^+ cation. These extra-framework cations play an important role in determining the adsorption, separation and catalytic properties of zeolite. The positive charge of extra-frame work cations produces electrostatic field within the zeolite pores, which can strongly influence adsorptive behavior and catalytic properties in activating polar reactant molecule.[23] Thus, mild acidic and basic nature of Na-Y zeolite facilitates nucleophilic attack of amine on methylene carbon of alkylene carbonate liberating CO_2 to give β- amino alcohol.

Table 4.2. Screening of catalysts for *N*-alkylation of aniline using ethylene carbonate



1 **2** **3** *N*-phenyl ethanolamine (NPEA) **4** *N*-phenyl diethanolamine (NPDEA)

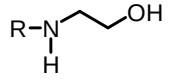
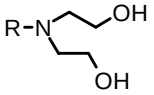
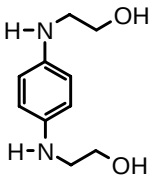
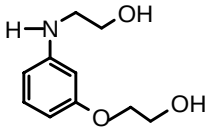
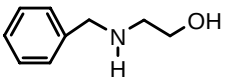
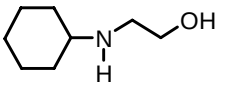
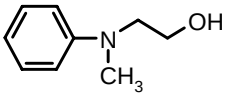
Entry	Catalyst	Time, (h)	Aniline conversion,[a] (%)	NPEA Yield,[a] (%)	NPDEA yield,[a] (%)
1	None	2	3.8	3.8	-
2	TEAB	2	82.5	68	14.5
3	PbO	2	10.7	10.7	-
4	ZnO	2	18.7	18.7	-
5	MgO	2	12.6	12.6	-
6	$CsCO_3$	2	15.7	2	-
7	$PbZrCO_3$	2	10.8	10.8	-
8	$PbCO_3$	2	13.3	11.2	-
9	Mg-Al HTLC	2	10	10	-
10	K+ on Silica	2	19.3	7.9	-
11	Na-ZSM5	2	4.3	4.3	-
12	KNO_3 on KL	2	19.2	7.8	-
13	4 Å MS	2	4.8	4.8	-
14	H-Y	2	28	28	-
15	Na-Y	0.5	100	100	-
16	Na-X	0.5	89.9	89.9	-
		2	100	95.7	4.3

Reaction conditions: aniline, 10.7 mmol; ethylene carbonate, 13 mmol; triglyme (solvent), 15.5 mol; catalyst, 1.8 mmol (entries 2-8) or 0.25 g (entries 9-16); T, 433 K; N_2 atmosphere; [a] conversion and yields were determined by GC analysis.

4.2.2.2. Synthesis of β-amino alcohols using various amines and ethylene carbonate

In order to increase the range of applicable substrates, the protocol was extended to a range of amines with different functional groups and results are presented in Table 4.3. It was noticed that aliphatic amines gave predominantly carbamates (Table 4.3, entry 10) while aromatic amines gave selectively β-amino alcohols which could be explained by HSAB theory.[2] Tundo et al.[24] also demonstrated this type of selectivity pattern for the dimethyl carbonate aminolysis reaction. The results were generally in agreement with the reactivity pattern expected for substituted anilines and most of screened anilines gave high yield of β-amino alcohols (> 90%). Electron donating substituents such as $-CH_3$, $-NH_2$ and $-OCH_3$ enhanced the nucleophilicity of aniline thus increasing the reactivity as well as yield of β-amino alcohols (entry 3-5), while electron withdrawing substituents such as -Cl, $-NO_2$ on aniline ring decreased the reactivity as well as the yield (entry 7-8). It was observed that, bis amino alcohols were formed at the cost of decreased selectivity of mono amino alcohol. The formation of bis derivative depended on concentrations of alkylene carbonate and mono amino alcohol. It was also observed that in the case of *p*-phenylene diamine and *m*-amino phenol, selectivity of mono amino alcohol decreased a little due to the further N or O- alkylation of $-NH_2$ and -OH groups present on aromatic amines respectively (Table 4.3, entry 5, 6).

Table 4.3. Synthesis of β-amino alcohols using ethylene carbonate

Sr. No	Amine	Time (h)	Amine conv. (%)	Yield (%) [a]		Side-products yields[a,b] (%)
						
1	Aniline	0.5	100	100 (94), **3**	-	-
2[c]	Aniline	0.5 2	100 100	93 72 (63)	7 28 (19), **4**	
3	*p*- toluidine	1.5	100	91(86), **3a**	9, **4a**	-
4	*p*-anisidine	1	100	93 (88), **3b**	7, **4b**	-
5	*p*-phenylene diamine	2	87	80 (70), **3c**	-	7, **8** 
6	*m*- amino phenol	2	100	93 (84), **3d**		8, **9** 
7	*p*- chloro aniline	12	100	98 (91), **3e**	2, **4e**	-
8	*p*- nitro aniline	12	61	40 (30), **3f**	-	21
9	Benzyl amine	2	100	40, **5** 	-	60
10[d]	Cyclohexyl amine	2	100	2, **6** 	-	98
11	*N*-methyl aniline	6	100	100 (93), **7** 	-	-

Reaction conditions: amine, 10.7 mmol; ethylene carbonate, 13 mmol; triglyme (solvent), 15.5 mol; Na-Y catalyst, 0.25 g (activated at 773 K for 6 h); T, 433 K; N_2 atmosphere; [a] yields were determined by GC analysis based on amine conversion and isolated yields are indicated in brackets. [b]side-products include 3-(4-nitrophenyl) oxazoliin-2-one(entry 8), 2-hydroxyethyl benzyl carbamate and 3-benzyloxazolidin-2-one (entry 9, 46 % and 14% yield respectively) and 2-hydroxyethyl cyclohexyl carbamate (entry 10); All side products were confirmed by GC-MS analysis but were not isolated. [c] Ethylene carbonate was used as solvent; [d] Reaction carried out at 407 K.

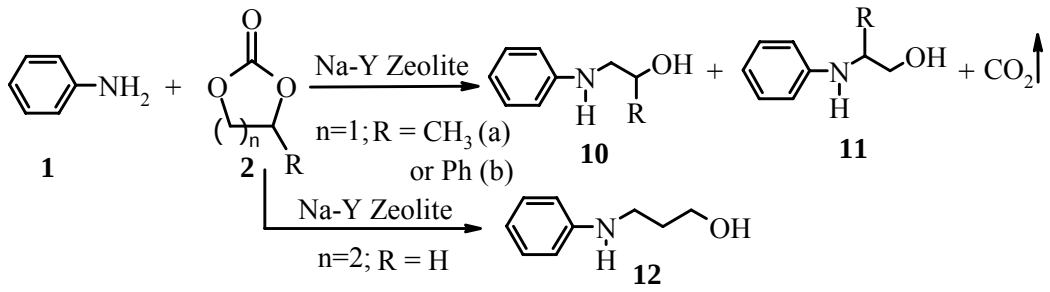
4.2.2.3. Synthesis of β-amino alcohols using various alkylene carbonates

To further test the activity of the Na-Y catalyst and applicability of the method, various alkylene carbonates were subjected to *N*-alkylation with aniline to furnish β-amino alcohols and the results are presented in Table 4.4. Quantitative yields of corresponding amino alcohols were obtained in the reaction of 1,2- propylene carbonate, styrene carbonate and 1,3- propylene carbonate with aniline. Regioselective ring opening reaction of unsymmetrical alkylene carbonates with amine by Na-Y catalyst was also evaluated. The corresponding amino alcohols from unsymmetrical cyclic carbonates were obtained in high yields but in case of 1,2 propylene carbonate, the regioisomers could not be separated by column chromatography hence; the regioselectivity was determined by GC and GC-MS analysis (Table 4.4, entry 1-5). As expected, an excellent regioselectivity of 92:8 (**10a:11a**) in favor of nucleophilic attack at the sterically less hindered methylene carbon of carbonate was observed affording 92% yield of 1-(phenyl amino)propan-2-ol (**10a**) during the reaction with 1,2 propylene carbonate (entry 1). It was also observed that the regioselectivity was slightly improved by lowering the reaction temperature (entry 2). Two regioisomers viz. 1-(phenyl amino) propan-2-ol (**10a)** showed the characteristic ion peak at m/z M^+ -45 due to loss of CH_3CHOH where as, 2-(phenyl amino) propan-1-ol (**11a)** showed the ion peak at m/z M^+ -31 due to loss of CH_2OH in mass spectra.[1b] While, in case of styrene carbonate, reverse regioselectivity was observed, in that the ratio of isomers observed was 9:91 (**10b:11b**, Table 4.4, entry 6). Selective formation of the regioisomeric product 2-phenyl amino-2-phenyl ethanol **(11b)** was observed due to the preferred attack of aniline nucleophile on benzylic carbon of styrene carbonate which

being a more stable carbonium ion. The regioisomers in this case were isolated in pure form using flash chromatography technique.

Excellent yield of 3-(phenylamino) propan-1-ol was realized from 1,3- propylene carbonate (Table 4.4, entry 7). It was also observed from the screening of alkylene carbonates that ethylene carbonate showed highest reactivity among the alkylene carbonates screened and the order of reactivity obtained was R= H > CH_3 > Ph which was consistent with that reported earlier.[13]

Table 4.4. Synthesis of β-amino alcohols using various alkylene carbonate

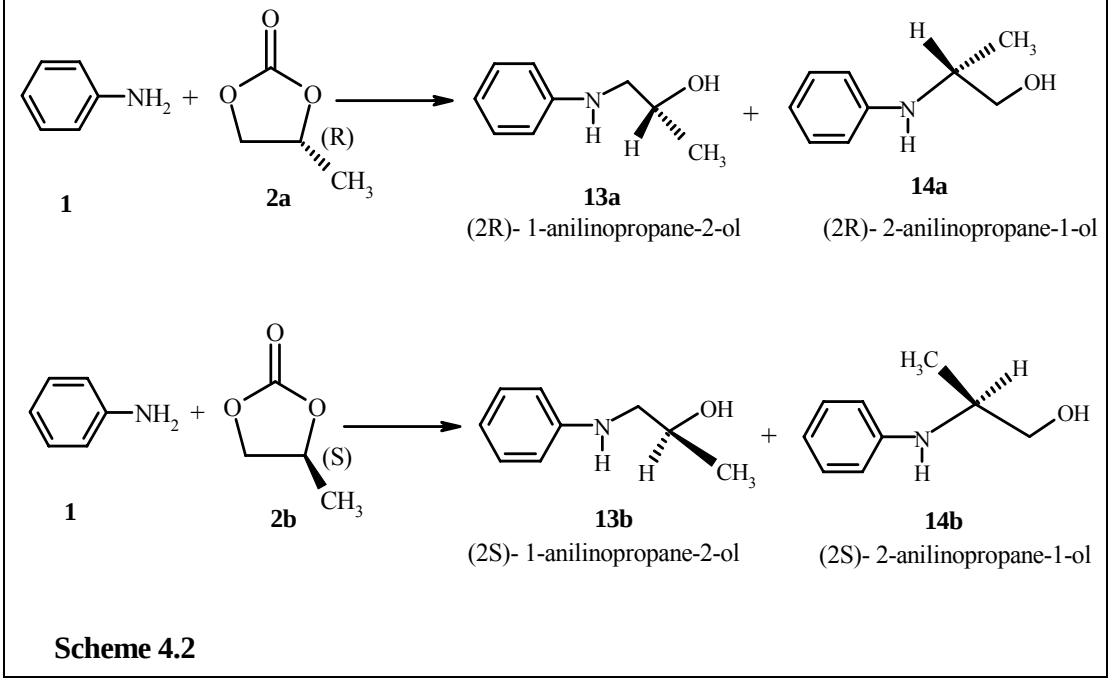


Entry	Cyclic carbonate	Time, (h)	Aniline conv. (%)[a]	(10:11)[b]	Isolated Yield (%)
1	1,2-propylene carbonate	7	100	92:8	90 (**10a+11a**)
2	1,2-propylene carbonate	72	100	96:4	90 (**10a+11a**)
3[b,c]	R (+) 1,2- propylene carbonate	72	100	96:4	92(**13a+14a**)
4[b,c]	S (-) 1,2- propylene carbonate	72	100	96:4	91(**13b+14b**)
5[b]	R (+) 1,2- propylene carbonate	7	100	92:8	91(**13a+14a**)
6	Styrene carbonate	8	100	9:91	3 (**10b**), 85 (**11b**)[25]
7	1,3- propylene carbonate	8	82	-	71 (**12**)

Reaction conditions: aniline, 10.7 mmol; alkylene carbonate, 13 mmol; triglyme (solvent), 15.5 mol; Na-Y catalyst, 0.25 g (activated at 773 K for 6 h); T, 433 K; N_2 atmosphere; [a] conversion was determined by GC analysis. [b] ratio of regioisomers was determined by GLC. [c] reaction was carried out at 371 K in toluene solvent

4.2.2.3.1. Synthesis of Chiral β-amino alcohols

Chiral β-amino alcohols were also synthesized from chiral carbonates using the same experimental procedure as mentioned in Section 4.2.1.2. Reaction of (R/S) 1,2-propylene carbonate (98% ee) with aniline gave four possible chiral β-amino alcohol products illustrated by reaction Scheme 4.2 as follows.



Scheme 4.2

Excellent yields of chiral β-amino alcohols were obtained from the reaction of aniline and chiral 1,2-propylene carbonates using Na-Y catalyst (Table 4.4, entry 3-5). It was observed that even at high temperature chiral amino alcohol can be synthesized using stable chiral 1,2-propylene carbonates. Schultze et al.[26] have also reported the use of chiral propylene carbonate in drastic condition employing highly basic media and high temperature. The four optical isomers (Scheme 4.2) were separated on chiral HPLC using racemic mixture of two regioisomers: (±)-1-anilino propane 2-ol and (±)-2-anilino propane 1-ol obtained from (±)-1,2-propylene carbonate as follows: chiral column: Dicel

chiral OD-H column; hexane:*i*-PrOH (97.5:2.5%, V/V), flow rate, 1 ml/min; t_1= 42.2 min, **14a (**minor**)**; t_2= 45.2 min, **13a** (major); t_3= 58.2 min, **13b** (major); t_4= 60.0 min, **14b (**minor**);** see Section on Spectra, page no. 218-220.

4.2.2.4. Catalyst recycling

The reusability of catalyst was studied. For that, reaction mixture was diluted with acetonitrile and then it was filtered through sartorius 393-grade filter paper to separate the catalyst. More washings of acetonitrile were given to it to remove adhered organic impurities. Then catalyst was dried at 773 K for 6 h in air. This catalyst was used for new reaction to study the catalyst recycle. The results on catalyst recycle experiments are depicted in the Figure 4.1. It showed that the catalyst was reusable and there was no loss in its catalytic activity at the end of fifth recycles.

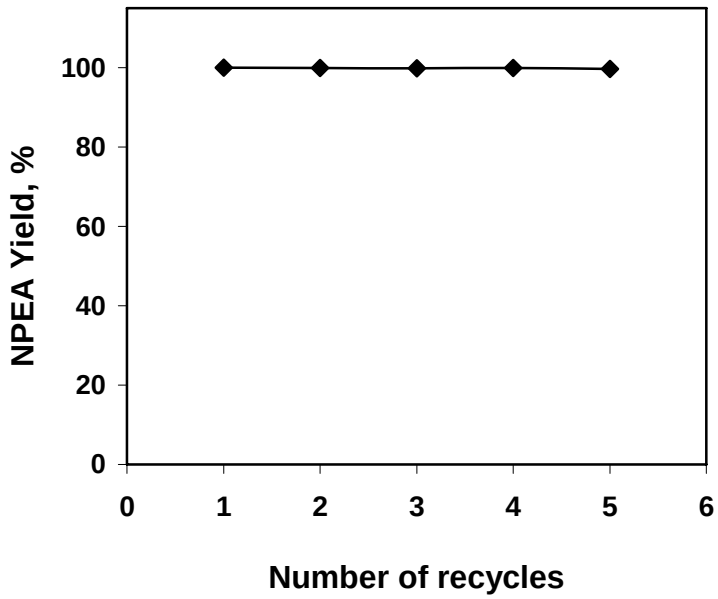


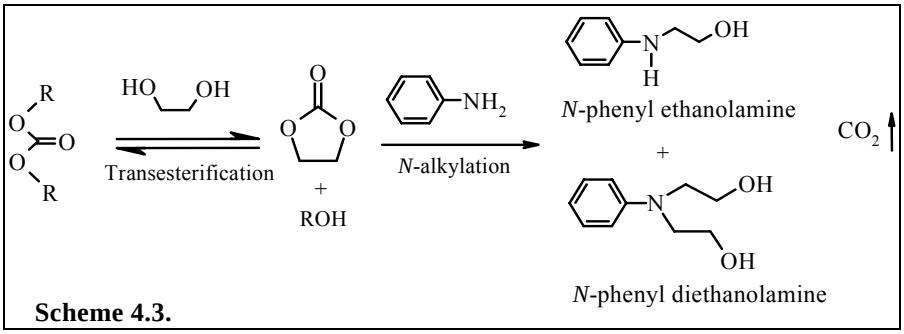
Figure 4.1. Na-Y catalyst recycles study

Reaction conditions: aniline, 10.7 mmol; ethylene carbonate, 13 mmol; triglyme (solvent), 15.5 mmol; Na-Y catalyst, 0.25 g; T, 433 K; Time, 0.5 h; N_2 atmosphere; Yield was determined by GC analysis.

4.3. TANDEM SYNTHEASIS OF β-AMINO ALCOHOL FROM AROMATIC AMINE, DIALKYL CARBONATE AND ETHYLENE GLYCOL

Tandem reactions link several transformations together in a single step. Wherein, an initial reaction produces an intermediate that undergoes further transformation with strategically positioned reactive centers in the same molecule, with other compounds in the reaction mixture, or with additional reagents introduced after the initial transformation takes place.[27] As the focus of chemical industry is to make specialty chemicals via simple and clean technology is gaining importance, tandem reactions would be one of the parts of clean processes. Because tandem reactions increase synthetic efficiency by decreasing the number of laboratory operations, quantities of chemicals, solvents, reagents and energy. Thus, these reactions would allow an environmentally and economically favorable production.

In this present work, tandem synthesis of β-amino alcohol from aromatic amines, dialkyl carbonate and ethylene glycol was demonstrated for the first time. In this synthesis, transesterification of dialkyl carbonate by ethylene glycol to ethylene carbonate and *N*-alkylation of aniline by ethylene carbonate to β-amino alcohol was conducted in a single step (Scheme 4.3). In-situ generation of ethylene carbonate avoids the isolation and purification steps involved in the synthesis of pure ethylene carbonate.



Scheme 4.3.

This reaction system was investigated in high-pressure as well as pot reaction conditions.

4.3.1. TANDEM SYNTHESIS OF β-AMINO ALCOHOL UNDER HIGH PRESSURE REACTION CONDITION

Various aspects such as catalyst screening, screening of dialkyl carbonates, catalyst loading effect, dialkyl carbonate concentration effect and temperature effect were studied to understand the effect of all these parameters on the conversion of amines and selectivity pattern of amino alcohols. High-pressure reactions were carried out for the synthesis of β-amino alcohols using following experimental procedure.

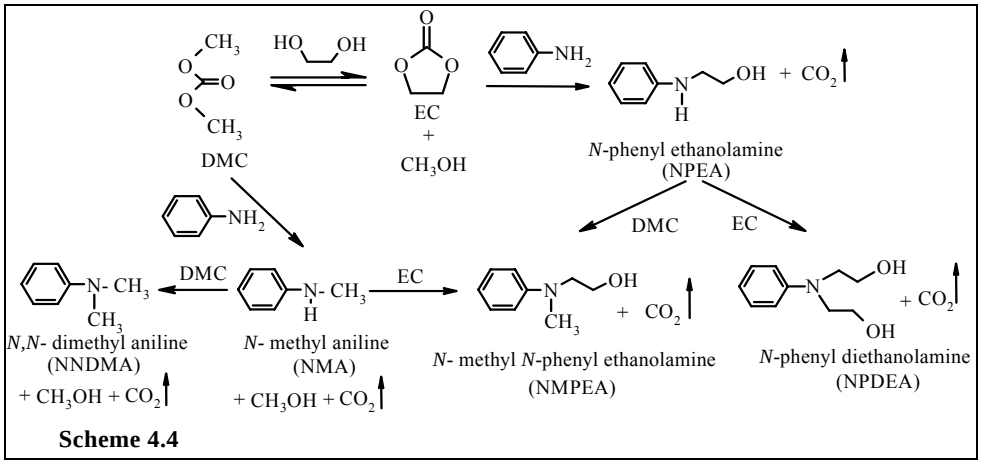
4.3.1.1. General experimental procedure for high-pressure reaction

High-pressure reactions were carried out in a parr autoclave (50 ml). In a typical experiment, known quantities of amine, dialkyl carbonate, ethylene glycol and catalyst were charged into the reactor. The reactor was flushed with nitrogen and then pressurized with nitrogen up to 3.4 MPa. Then the contents were heated to the required temperature and the progress of the reaction was monitored by withdrawing the intermediate samples which were quantitatively analyzed by GC for reactants and products. The reaction was continued for specified time, the contents were cooled to room temperature and gas vented off. Liquid phase analysis was carried out using same GC programme given in Section 4.1.2.3.

4.3.1.2. Preliminary experiments for catalyst screening

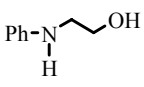
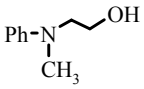
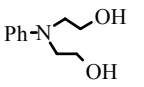
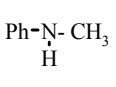
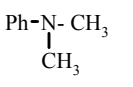
Transesterification[28] and *N*-alkylation [14] reactions are well known in the literature. Generally both acid and base catalysts are effective for transesterification; however base catalysts are often employed for *N*-alkylation of amines as well as for

transesterification.[29] Therefore, for the purpose of preliminary catalyst screening a few basic catalysts were tested for the reactions of aniline, dimethyl carbonate (DMC) and ethylene glycol (EG) and the results are shown in Table 4.5 and possibilities of reactions are shown in Scheme 4.4. In the absence of a catalyst there was no reaction (Table 4.5, entry 1). From the catalyst screening, it was observed that basic catalysts like, dibutyl tin oxide (DBTO), tetraethyl ammonium bromide (TEAB), $PbCO_3$ and ZnO showed activity for the tandem reaction, giving rise to *N*-phenyl ethanolamine (NPEA) up to 20-50% yield (entry 2-5). Zeolites, such as Na-Y and Na-X were also tested for this reaction and it was found that both the catalysts gave good yield of NPEA (~ 50%, entry 6, 7) while Na-Y gave better conversion than Na-X (~ 92%, 7). Soluble catalysts, TEAB was more selective for methylated amino alcohol as well as bis-amino alcohol, while DBTO showed preference for methylated anilines and amino alcohol (entry 2 and 3 respectively). Catalysts $PbCO_3$ and ZnO showed good selectivity for NPEA (~ 70%, entry 4, 5) but activity of these catalysts was poor compared to Na-Y zeolite. In order to check the possibility of formation of β-amino alcohol from the condensation reaction of aniline and ethylene glycol, an experiment was carried out in presence of Na-Y catalyst without DMC, wherein β-amino alcohol was not formed (entry 8).



Scheme 4.4

Table 4.5. Screening of catalysts for the reaction of aniline, DMC and EG

Sr. No.	Catalyst	Aniline conv. (%)	Yield,[a,b] (%)				
							
1	none	0	0	0	0	0	0
2	DBTO	68.2	18.1	25.9	9.3	8.7	6.2
3	TEAB	95	24.9	36.9	24.1	1.12	3.44
4	$PbCO_3$	74	49	12	10.4	2.6	0
5	ZnO	78	43.6	12.9	11.2	6.8	3.5
6	Na-X	86.5	49.7	23.3	5.4	5	3.1
7	Na-Y	92.3	51.1	26.5	8.6	2.8	3.3
8[c]	Na-Y	0	0	0	0	0	0

Reaction conditions: aniline, 10.7 mmol; DMC, 33 mmol; ethylene glycol, 286 mmol; catalyst, 2.3 mmol (entry 2-5), 0.25 g (entry 6-8); T, 443 K; N_2 pressure, 3.4 MPa; agitation speed, 13 Hz; Time, 2 h; reaction volume, 20 ml; [a] yields were determined by GC analysis and based on aniline conversion, [b] products were confirmed by GC-MS; [c] in absence of DMC

A typical progress profile of the reaction of aniline, dimethyl carbonate and ethylene glycol for synthesis of β-amino alcohol using Na-Y zeolite catalyst is shown in Figure 4.2 (Concentration profiles of DMC and EG is not shown for the sake of convenience). Complete conversion of aniline was achieved at the end of 4h and correspondingly DMC and EG was also consumed with concurrent formation of amino alcohols and *N*-methylated anilines. Material balance was in complete agreement with the products formed as shown in Scheme 4.4. The figure showed that *N*-phenyl ethanolamine was rapidly formed (61%) in the beginning of the reaction. NPEA was formed from the reaction of aniline and ethylene carbonate (generated in-situ by transesterification reaction of DMC and ethylene glycol). Thereafter yield of NPEA decreased due to further reaction of NPEA with EC and DMC to give *N*-phenyl diethanolamine (NPDEA) and *N*-methyl *N*-phenyl ethanolamine (NMPEA) respectively (Scheme 4.4). Usually reaction of

aniline with dimethyl carbonate is known to give *N*-alkylated products (mono and dimethyl anilines) at higher reaction temperature.[14] However, in presence of ethylene glycol, reaction pattern of aniline and dimethyl carbonate was altered and dimethyl carbonate reacted more readily with ethylene glycol instead of aniline forming ethylene carbonate. Hence, low yields of *N*-methyl aniline (NMA) and *N,N*-dimethyl aniline were realized compared to amino alcohols.

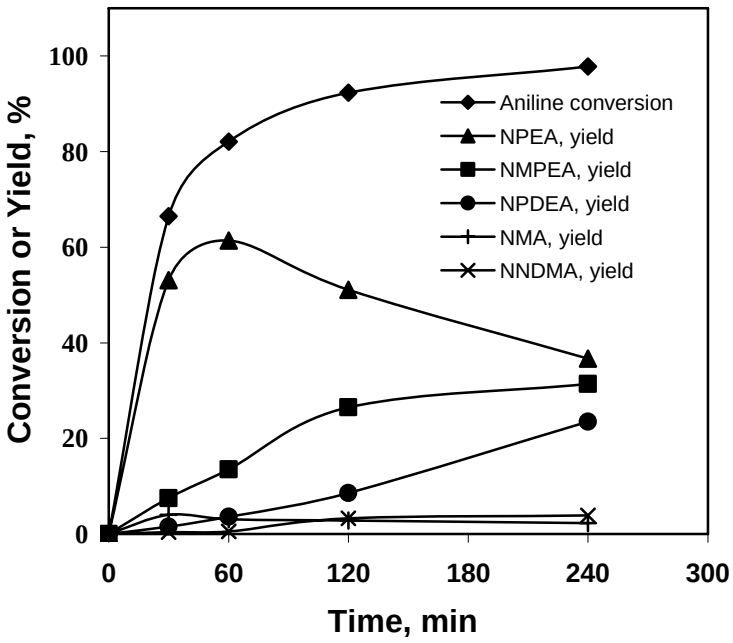


Figure 4.2. Progress profile of the pressure reaction with time

Reaction conditions: aniline, 10.7 mmol; DMC, 33 mmol; ethylene glycol, 286 mmol; Na-Y zeolite catalyst, 0.25 g; T, 443 K; N_2 pressure, 3.4 MPa; agitation speed, 13 Hz; Time, 4 h; reaction volume, 20 ml.

4.3.1.3. Effect of catalyst loading

The effect of Na-Y zeolite catalyst loading on the yield of β-amino alcohols is shown in Figure 4.3. The figure showed that catalyst loading had mild effect on conversion and yields of amino alcohols in the loading range investigated. However, it can be seen that initially yield of *N*-phenyl ethanolamine increased up to 51% and then it

decreased sharply as catalyst loading was increased with concurrent formation of NPDEA and NMPEA. Usually linear dependency of conversion with catalyst loading was expected, however in the present case, the tandem nature of reaction probably made the catalyst loading effect more complex in nature (Scheme 4.4).

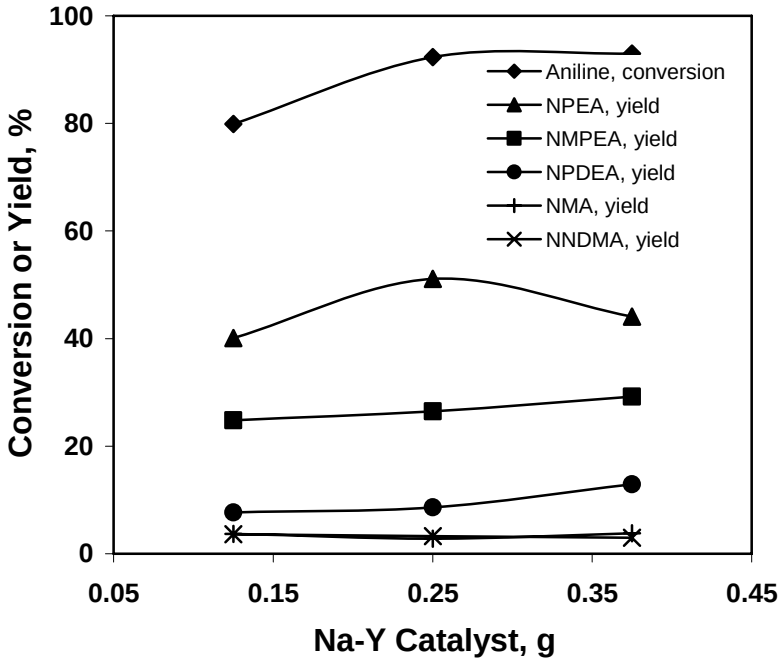


Figure 4.3. Effect of catalyst loading

Reaction conditions: aniline, 10.7 mmol; DMC, 33 mmol; ethylene glycol, 286m mol; Na-Y zeolite catalyst; T, 443 K; N_2 pressure, 3.4 MPa; agitation speed, 13 Hz; Time, 2 h; reaction volume, 20 ml.

4.3.1.4. Effect of temperature

The temperature effect was investigated in the range of 423-453 K and the results are shown in Figure 4.4. The figure showed that conversion of aniline and yields of NMPEA and NPDEA increased with increase in temperature. While, yield of NPEA passed through maximum due to it's further conversion to NPDEA and NMPEA with increase in temperature. Thus, higher temperature favors formation of NMPEA and NPDEA.

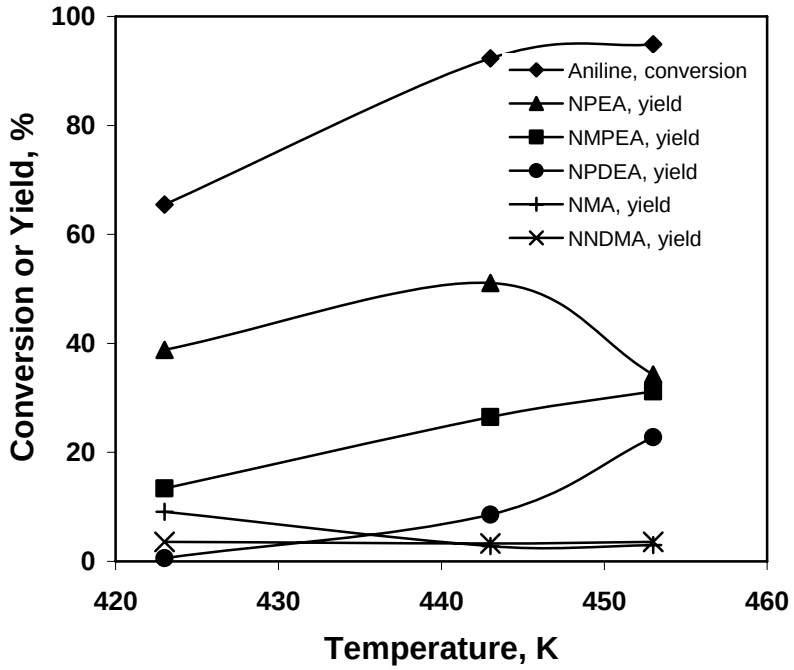


Figure 4.4. Effect of temperature

Reaction conditions: aniline, 10.7 mmol; DMC,33 mmol; ethylene glycol, 286 mol; Na-Y zeolite catalyst, 0.25 g; N_2 pressure, 3.4 MPa; agitation speed, 13 Hz; Time, 2 h; reaction volume, 20 ml.

4.3.1.5. Effect of dimethyl carbonate concentration

Dimethyl carbonate played a key role on yields of amino alcohol derivatives, since DMC was involved in various reactions that took place under experimental conditions investigated in this study (Scheme 4.4). The effect of DMC concentration on the yield of mono β-amino alcohol was investigated in the range of 0.81–3.24 × 10^{-3} mol/cm^3 (Figure 4.5). Figure showed that there was no much increase in NPEA yield as DMC concentration increased from 0.81-1.62 × 10^{-3} mol/cm^3. But as the DMC concentration increased from 1.62 – 3.24 × 10^{-3} mol/cm^3, there was sharp decrease in NPEA yield. While, yield of *N*-methyl *N*-phenyl ethanolamine increased sharply as DMC concentration was increased. Possibility of NMPEA formation can be realized via two path ways (Scheme 4.4), in first path NPEA is further methylated by DMC and in second

case *N*-methyl aniline undergoes *N*-alkylation by EC giving rise to NMPEA. However, from the figure it is clearly seen that major contribution of NMPEA formation is via N-methylation of NPEA as yield profile of NPEA shows sharp decline with simultaneous increase in NMPEA yield. Whereas NMA yield profile was not much changed during this period. Therefore, high DMC concentration gave selective formation of NMPEA.

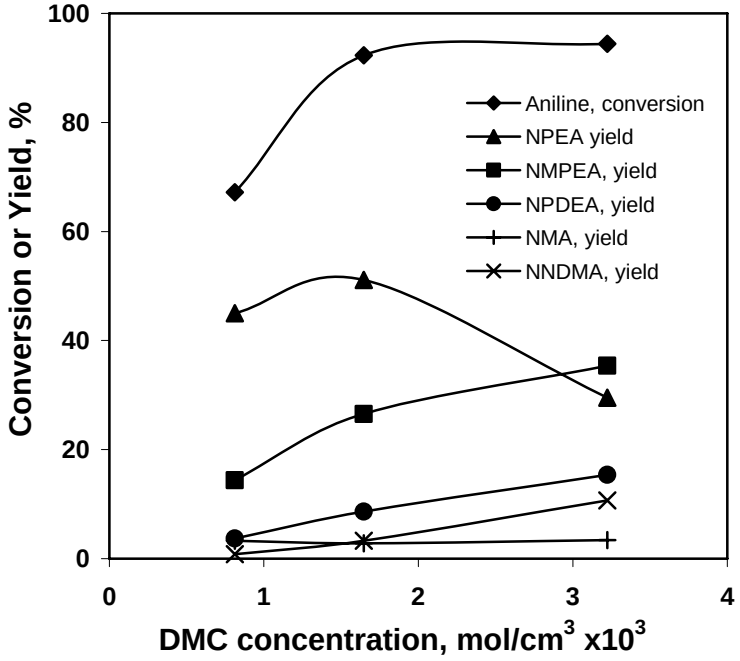


Figure 4.5. Effect of DMC concentration

Reaction conditions: aniline, 10.7 mmol; DMC; ethylene glycol, 286 mmol; Na-Y zeolite catalyst, 0.25 g; T, 443 K; N_2 pressure, 3.4 MPa; agitation speed, 13 Hz; Time, 2 h; reaction volume, 20 ml.

4.3.1.6. Effect of dialkyl carbonates

Various dialkyl carbonates viz. dimethyl carbonate (DMC), diethyl carbonate (DEC) and dibutyl carbonate (DBC) were investigated for the tandem synthesis of β-amino alcohol reaction to see their transesterification efficiency to form ethylene carbonate as well as reactivity towards *N*-alkylation of anilines (Figure 4.6). Figure showed that DMC was the most reactive among the screened dialkyl carbonate but least

selective for giving *N*-phenyl ethanolamine (because of its better methylating ability). While, DEC and DBC gave selectively NPEA and highest selectivity was obtained with DBC, however yield of NPEA was greater with DEC (Figure 4.6).

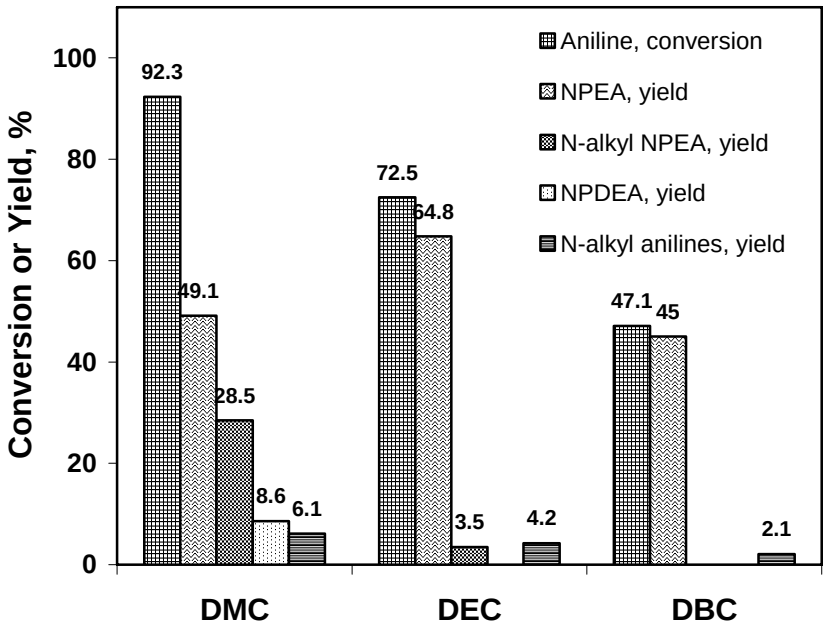


Figure 4.6. Effect of dialkyl carbonates

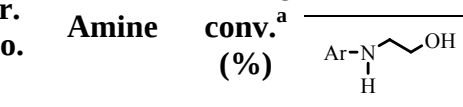
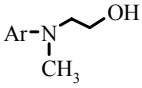
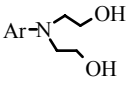
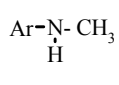
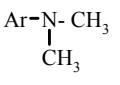
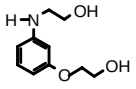
Reaction conditions: aniline, 10.7 mmol; dialkyl carbonate, 33 mmol; ethylene glycol, 286 mmol; Na-Y zeolite catalyst, 0.25 g; T, 443 K; N_2 pressure, 3.4 MPa; agitation speed, 13 Hz; Time, 2 h; reaction volume, 20 ml.

4.3.1.7. Effect of amines

Various amines were screened for tandem synthesis of β-amino alcohol from DMC and EG using Na-Y zeolite catalysts and results are presented in Table 4.6. It was observed that most of the amines showed higher conversions (> 92%) except *p*-chloro aniline and *p*-nitro aniline (Entry 4 & 5). The results are generally in agreement with the reactivity pattern expected for substituted aromatic amines. Electron-donating substituents such as $–CH_3$, $–OCH_3$ enhance the nucleophilicity of aniline thus increasing the reactivity as well as total yield of amino alcohols (total yield of amino alcohol

includes yield of mono β-amino alcohol, methylated amino alcohol and bis-amino alcohol; Entry 2-3). While electron-withdrawing substituents such as –Cl, $–NO_2$ on the aniline ring decreases the reactivity as well as yield of amino alcohols (Entry 4 & 5). It was observed that in most of the screened amines, mono β-amino alcohols were not formed selectively wherein methylated amino alcohols and bis-amino alcohols were also formed. In case of *m*-amino phenol, both *N*-alkylation as well as *O*-alkylation by ethylene carbonate was observed (Entry 6). While in case of benzyl amine, oxazolidones and carbamates were formed in substantial amounts along with amino alcohols (Entry 7). Since, benzyl amine is a stronger nucleophile[30] than anilines; benzyl amine can effectively attack both the electrophilic carbons of ethylene carbonate, viz. carbonyl carbon (which is hard) and methylene carbon (which is soft). Thus benzyl amine which was neither too soft nor too hard in nature was able to react with both the reactive centers of ethylene carbonate in accordance with HSAB theory. The reaction of benzyl amine with soft electrophilic carbon gives rise to β-amino alcohols while reaction with hard electrophilic carbon produced 2-hydroxyethyl benzyl carbamate and 3-benzyloxazolidin-2-one (See Table 4.6, entry7, 12.3% and 36.7% respectively). It may however be noted that, the explanation given here is qualitative in nature as applicability of nucleophilicity is much more complicated than described here.[31]

Table 4.6. Synthesis of β-amino alcohols from various amines using DMC and EG

Sr. No.	Amine	Amine conv.[a] (%)	Yield,[a,b] (%)				
							
1	Aniline	92.3	51.1	26.5	8.6	2.8	3.3
2	*p*-toludine	99.8	27.5	45.5	17.3	1.3	8.2
3	*p*-anisidine	100	34.5	28	29.8	0	7.7
4	*p*-chloro aniline	69	40.6	14.5	0.3	9.9	3.7
5	*p*-nitro aniline	2	0	0	0	1.5	0
6	*m*-amino phenol	100	35.6	28.4	15.6 	3.9	9.2
7	Benzyl amine[c]	99	16	21	0	0	1.2

Reaction conditions: amine, 10.7 mmol; DMC, 33 mmol; EG, 286 mmol; Na-Y catalyst, 0.25 g; T, 443 K; N_2 pressure, 3.4 MPa; agitation speed, 13 Hz; Time, 2 h; reaction volume, 20 ml; [a] conversion and yields were determined by GC analysis, [b] products were confirmed by GC-Ms; [c]2-hydroxyethyl benzyl carbamate (12.3%) & 3-benzyloxazolidin-2-one (36.7%) were formed as side product.

From the investigation of the tandem synthesis of β-amino alcohol from aniline, dimethyl carbonate and ethylene glycol under high-pressure reaction conditions, it was concluded that all three amino alcohols viz. *N*-phenyl ethanolamine; *N*-methyl-*N*-phenyl ethanolamine and *N*-phenyl diethanolamine were formed simultaneously.

4.3.2. TANDEM SYNTHESIS OF β-AMINO ALCOHOL UNDER POT REACTION CONDITION

For the tandem synthesis of β-amino alcohols from amine, dialkyl carbonate and ethylene glycol, following experimental procedure was used.

4.3.2.1. General experimental procedure

In a typical experimental procedure, known quantities of amine, diethyl carbonate and ethylene glycol were charged to a dried three necked 100 ml round bottom flask equipped with temperature controller, stirrer and fractional distillation assembly and this experimental set up is shown in Figure 4.7. The contents were flushed with nitrogen and heated at 399 K until the reflux of DEC commences, thereafter, the temperature was slowly raised to 418 K in 3 h. During this period, transesterification of ethylene glycol to ethylene carbonate occured due to the effective removal of ethanol (for DMC as substrate, transesterification was carried out in the range of 363 K to 398 K for 6 h). Excess of DEC was removed by increasing the temperature steadily from 418 K to 433 K in 0.5 h. After the complete removal of DEC, the reaction was continued for 4 hours at 433 K. A similar reaction procedure was followed for DBC as a substrate in which DBC being a high boiler (b.p. = 480 K) could not be distilled out. Reaction was monitored by time sampling and liquid phase was quantitatively analyzed using a gas chromatography.

Isolation of products: After the completion of reaction, reaction mixture was cooled at room temperature and filtered to separate the catalyst. Water was added to the filtrate and it was extracted with diethyl ether (3 × 15 ml). The ether layer was dried over anhydrous Na_2SO_4 and concentrated. The products were separated from concentrated organic phase by flash chromatography on a 4 g normal phase silica RediSep column employing n-

hexane-ethyl acetate as an eluent with gradient programming. The products were confirmed by GC-MS, IR, ^{1}H & ^{13}C NMR.

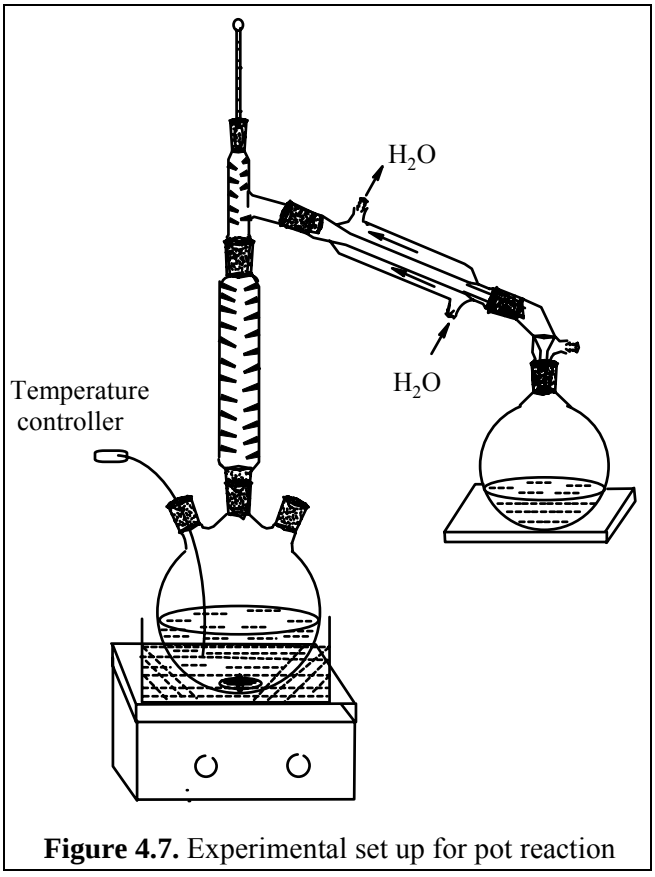


Figure 4.7. Experimental set up for pot reaction

4.3.2.2. Catalyst Screening

The screening of catalysts under pot condition was performed using both DMC and DEC as transesterification agent. This was thought necessary as DMC was more efficient towards transesterification and *N*-methylation of aniline than DEC, while DEC was more selective for NPEA formation (discussed in Section 4.3.1.6). Hence, it is important to observe the efficiency of various catalysts for *N*- alkylated amino alcohols formation (Scheme 4.4). Figure 4.8A and 4.8B showed the formation of amino alcohols

and *N*-alkylated anilines when DMC and DEC were used as transesterification agents respectively. From the catalyst screening, it was observed that basic catalysts like, ZnO, $PbCO_3$, tetraethyl ammonium bromide and dibutyl tin oxide showed good activity for the tandem reaction, giving rise to *N*-phenyl ethanolamine up to 30–60% yield (Figure 4.8A & 4.8B).

Zeolites, such as Na-Y and Na-X were also tested for this reaction and it was found that Na-X gave moderate yield of NPEA (Figure 4.8A & 4.8B, 55-70 %) while Na-Y gave excellent yield of NPEA in presence of DEC (Figure 4.8B, yield ~ 91%). It was also noticed that solid base zeolite catalysts were more selective towards NPEA formation (Figure 4.8A & 4.8B) compared to TEAB and $PbCO_3$. Formation of *N*-methyl aniline was at its maximum with TEAB as catalyst and DMC as transesterification agent (Figure 4.8A, ~19% yield of *N*-methyl aniline). On the other end, DEC as transesterification agent was more selective for NPEA synthesis and negligible *N*-ethyl aniline was seen with Na-Y as catalyst. When DMC was used as transesterification agent, $PbCO_3$ and DBTO gave rise to 12-14% yield of NPDEA, however, when DEC was used as transesterification agent $PbCO_3$ and TEAB were found to give rise to 7-9% yield of NPDEA (Figure 4.8B). Thus, these results suggested that high yield of β-amino alcohol was obtained using Na-Y catalyst and DEC was the best transesterification reagent for tandem synthesis of β-amino alcohols from ethylene glycol and aniline.

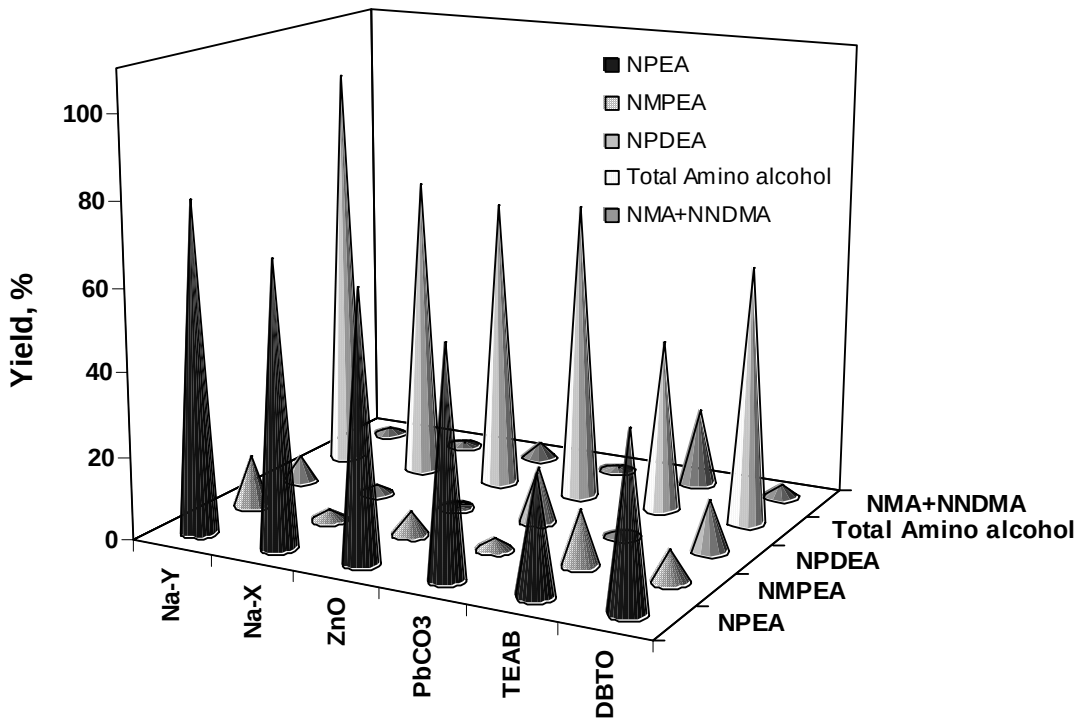


Figure 4.8A. Catalyst screening under pot reaction condition for DMC as transesterification agent

Reaction conditions: aniline, 10.7 mmol; dimethyl carbonate, 33 mmol; ethylene glycol, 286 mmol; catalyst, 2.3 mmol (ZnO, $PbCO_3$, TEAB, DBTO) or 0.25 g (Na-Y, Na-X zeolite); T, 363−433 K; Time, 9.5 h; reaction volume, 20 ml.

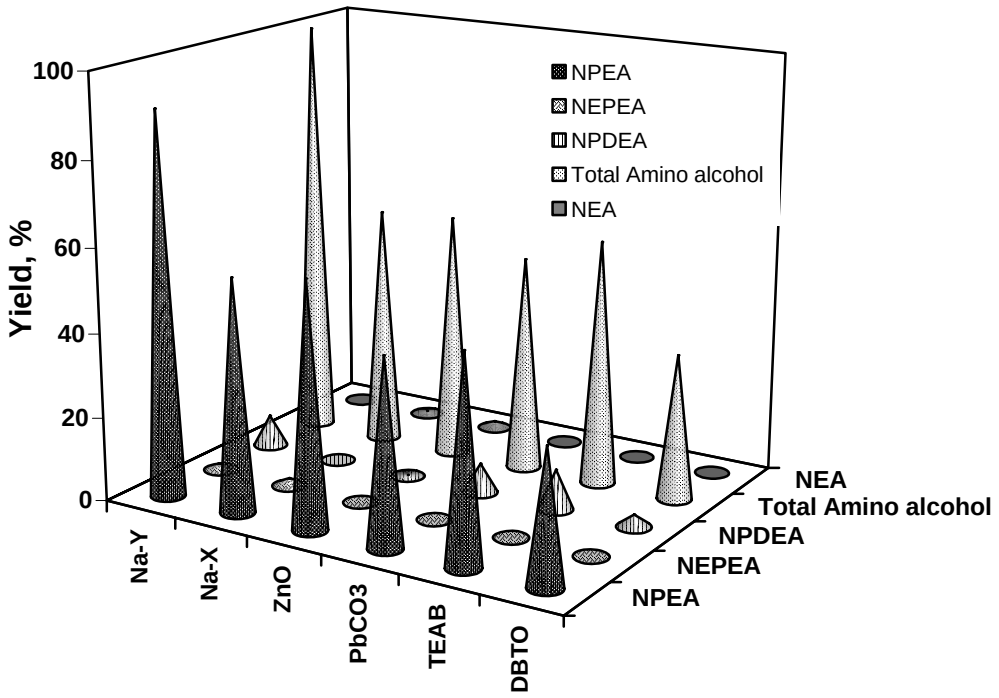


Figure 4.8B. Catalyst screening under pot reaction condition for DEC as transesterification agent

Reaction conditions: aniline, 10.7 mmol; diethyl carbonate, 33 mmol; ethylene glycol, 260 mmol; catalyst, 2.3 mmol (ZnO, $PbCO_3$, TEAB, DBTO) or 0.25 g (Na-Y, Na-X zeolite); T, 399−433 K; Time, 7.5 h; reaction volume, 20 ml.

A time concentration profile (Figure 4.9, in this figure, for the sake of convenience, concentration profile of DEC and EG was not shown) of this reaction showed that during transesterification step (399 K to 398 K in 3 h) along with ethylene carbonate, *N*-phenyl ethanolamine was also formed to the extent of 37% yield along with 1.5% yield of *N*-ethyl aniline (NEA). At this stage excess of DEC was distilled out within 0.5 h, meanwhile the reaction temperature was raised from 398 K to 433 K, where upon conversion of aniline and yield of NPEA increased with time. It was observed that as the concentration of NPEA increased, it further reacted with EC to give *N*-phenyl

diethanolamine and simultaneously *N*-ethyl aniline reacted with EC to give *N*-ethyl *N*-phenyl ethanolamine (NEPEA). In order to see, if the yields of bis-amino alcohol (NPDEA) can be further increased, a fresh lot of DEC (0.016 mol) was injected slowly at 7.5h to reaction mixture via dosing pump and reaction continued further up to 12.5h. A maximum yield of 92% NPDEA was realized (Figure 4.10).

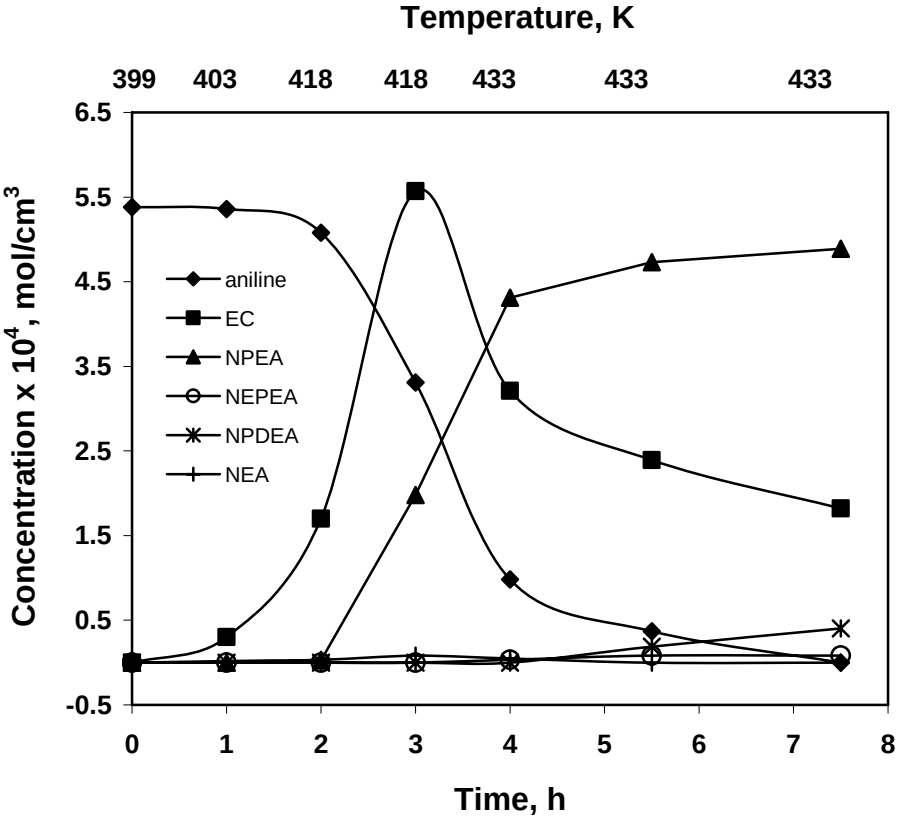


Figure 4.9. Concentration-Time profile of the reaction of aniline, DEC and ethylene glycol

Reaction conditions: aniline, 10.7 mmol; diethyl carbonate, 33 mmol; ethylene glycol, 286 mmol; Na-Y zeolite catalyst, 0.25 g (activated at 773 K for 6 h); Time, 7.5 h; reaction volume, 20 ml.

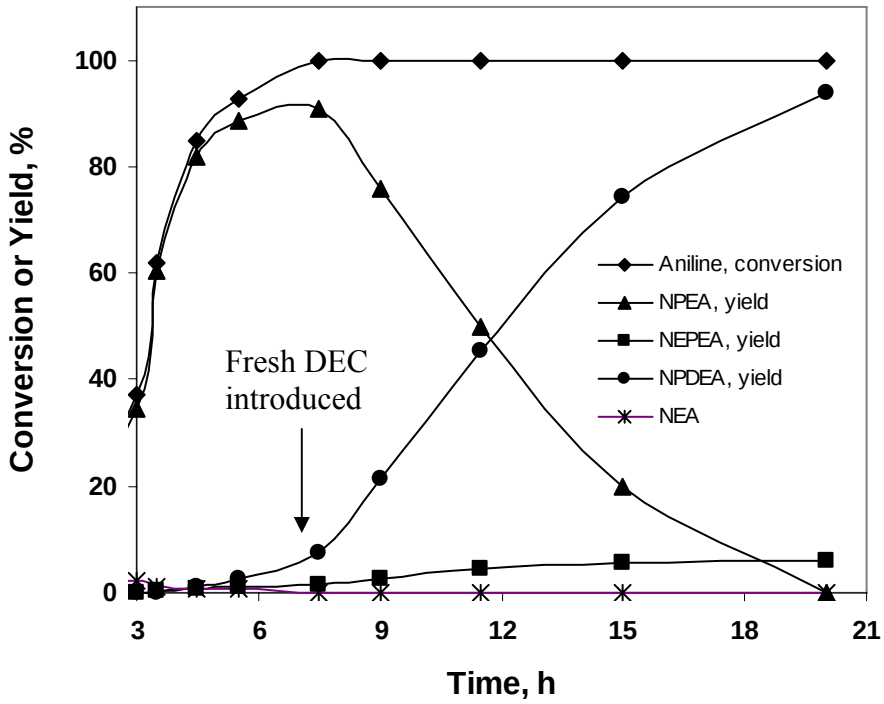


Figure 4.10. Synthesis of *N*-phenyl diethanolamine (NPDEA)

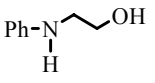
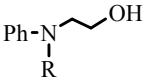
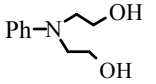
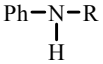
Reaction conditions: aniline, 10.7 mmol; diethyl carbonate, 33 mmol; ethylene glycol, 260 mmol; Na-Y zeolite catalyst, 0.25 g; After 7.5 h, 16 mmol diethyl carbonate was added and reaction was continued for 12.5 h.

4.3.2.3. Effect of dialkyl carbonates

Various organic carbonates such as dimethyl carbonate (DMC) and dibutyl carbonate (DBC) were also examined for this tandem reaction (Table 4.7). It was observed that, in case of dimethyl carbonate, 100% conversion of aniline was achieved with 79.5% yield of NPEA (entry 1). However, during transesterification step *N*-alkylation of aniline by DMC gave rise to *N*-methyl aniline in appreciable amounts which further undergoes alkylation by EC to give *N*-methyl *N*-phenyl ethanolamine (entry 1, 12.6% yield). *N*-alkylation of NPEA by EC to form NPDEA was also observed (entry 1, 6.4% yield). Both these reactions decreased the yield of NPEA (entry 1, 79.5% yield). When diethyl carbonate was used as a substrate, appreciably less amount of *N*-ethyl

aniline was formed during transesterification step because diethyl carbonate was not a good *N*-alkylating agent as compared to dimethyl carbonate [32] and NPEA was formed in high yields (91%, entry 2). While, dibutyl carbonate as transesterification agent gave lower yield of NPEA in (56.5%, entry 3), however in this case *N*-butyl aniline and *N*-butyl *N*-phenyl ethanolamine were not observed.

Table 4.7. Effect of organic carbonate on the synthesis β-amino alcohols

Sr. No.	Dialkyl carbonate	Aniline conversion[a] (%)	Yield,[a] (%)			
						
1[b]	DMC	100	79.5	12.6; **7**	6.4	0.9
2	DEC	100	91	1.5	7.5	0
3	DBC	57	56.5	0	0.5	0

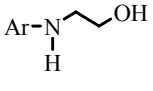
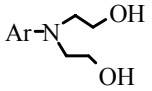
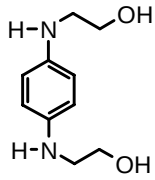
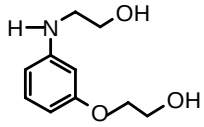
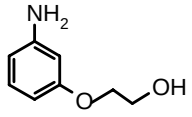
Pot reaction conditions: aniline, 0.0107 mol; dialkyl carbonate, 0.033 mol; ethylene glycol, 0.286 mol; Na-Y catalyst, 0.25 g; T, 399-433 K; Time, 7.5 h; [a] conversion and yields were determined by GC analysis; [b] T, 363-433 K; Time, 9.5 h

4.3.2.4. Effect of aromatic amines

In order to exemplify the wider range of applicability of the route, different types of amines were examined for β-amino alcohols synthesis from EG and DEC using Na-Y zeolite catalyst and results are presented in Table 4.8. The different reactivities of aromatic amines were dependent on substituents of the benzene ring. *p*-toluidine, *p*-anisidine and *p*-phenylene diamine having electron donating groups present on benzene ring facilitated the rate of reaction and β-amino alcohols were obtained in excellent yield (entry 2-4). It was also observed in these anilines that continuing the reaction for longer contact time, further *N*-alkylation of amino alcohol by ethylene carbonate was taking

place to give bis-amino alcohol (entry 1-3). While *p*- chloro aniline and *p*- nitro aniline having electron withdrawing groups present on benzene ring decreased rate of reaction and poor yield of β-amino alcohols were obtained (entry 6-7). In most of the screened amines, *N*-ethylated amino alcohol and *N*-ethylated aniline were also formed in lower yield and their combined yield was in the range of 1.5 to 3.7% (Table 4.9, last column, entry 1-4). It was also observed that in the case of *p*-phenylene diamine and *m*-amino phenol, the selectivity of mono-amino alcohol decreased due to further N- or O-alkylation of $–NH_2$ and –OH groups present on the aromatic amines (Entry 4 and 5). A different selectivity pattern was observed when *m*-amino phenol was used as a substrate. In this case, there is a possibility of *N* as well as *O*-alkylation by ethylene carbonate. But it was observed that *O*-alkylated product viz. 2-(3-aminophenoxy)ethanol (**17**) prevailed (56.8%, Table 4.9, entry 5) over *N*-alkylated product i.e 3-(2-hydroxyethylamino)phenol (**3d**; 5.8%), while 2-{[3-(2-hydroxyethoxy) phenyl]amino}ethanol (**16**) was formed as a result of both *N* and *O*-alkylation (27%).

Table 4.8. Effect of aromatic anilines on the synthesis β-amino alcohols

Sr. No.	Amine	Time (h)	Amine conv.[a] (%)	Yield[a] (%)		Side-product Yield[a, b] (%)
						
1	Aniline	4	81.7	80.2; **3**	0; **4**	1.5
		7.5	100	91	7.5	1.5
2	*p*-toluidine	3	85.8	84; **3a**	0; **4a**	1.8
		3.5	89.4	76.5	11.1	1.8
		5	100	68.8	29.4	1.8
3	*p*-anisidine	3	82.5	79.1; **3b**	0; **4b**	3.4
		4	100	81.5	15.1	3.4
4	*p*-phenylene diamine	3	84.2	80.5; **3c**	0; **15**	3.7
		4	100	73.2	23.1 	3.7
5	*m*-amino phenol	3.5	74.5	11.7; **3d**	19; **16**	43.8; **17**
		4.5	89.6	5.8	27 	56.8 
6	*p*-chloro aniline	6	64	64; **3e**	0; **4e**	0
		9	88	82.8	5.2	0
7	*p*-nitro aniline	7.5	2	1.2; **3f**	0	0

Pot reaction conditions: amine, 0.0107 mol; diethyl carbonate, 0.013 mol; ethylene glycol, 0.286 mol; Na-Y catalyst, 0.25 g; T, 399-433 K; [a] yields and conversions were determined by GC analysis, [b] side-products were confirmed by GC-MS, where side products corresponding to entry 1-4 are N-ethyl anilines and N-ethylated β-amino alcohols.

4.3.2.5. Catalyst recycles study

From the industrial point of view, one of the most intriguing aspects is the reusability of catalyst. The results of the catalyst reusability studies are given in Figure

4.11. After completion of the experiment, Na-Y catalyst was separated by filtration through Sartorius 393-grade filter paper. Separated catalyst was washed several times with acetonitrile to remove adhered organic impurities. The catalyst was dried at 373 K and then subjected to calcination at 773 K for 6 h in air and reused. The catalyst was recycled five times and it was observed that there was no loss in its catalytic activity and at the end of fifth recycle ~ 98% yield of amino alcohols were obtained (yield of NPEA ~ 90%). There were losses during handling since the particles were fine (~600-750 nm) and typically about 15-20% catalyst was lost during five recycles and these losses were accounted for activity calculations.

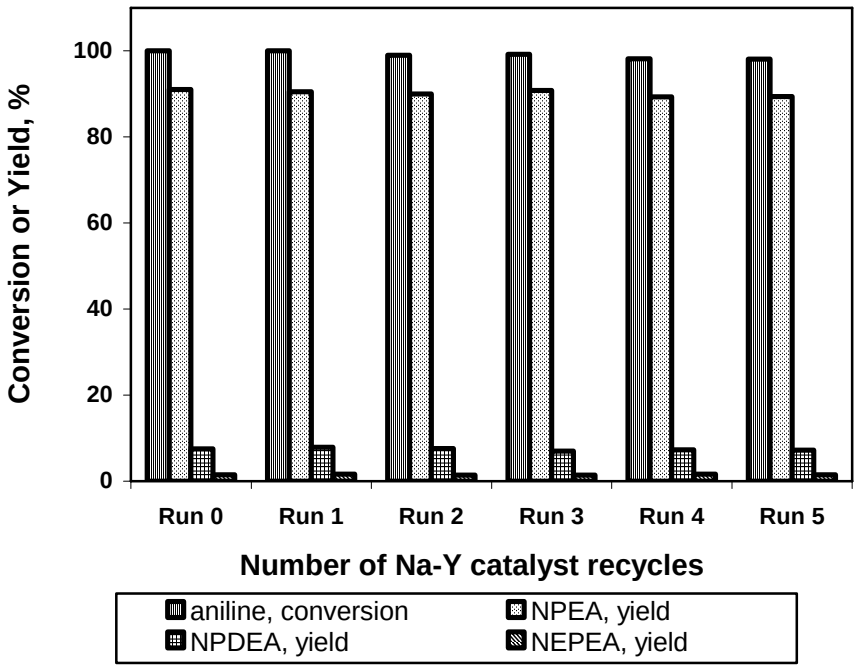


Figure 4.11. Na-Y zeolite catalyst recycles study for the tandem reaction

Reaction conditions: aniline, 0.0107 mol; diethyl carbonate, 0.033 mol; ethylene glycol, 0.286 mol; Na-Y zeolite catalyst, 0.25 g; Time, 7.5 h; reaction volume, 20 ml

4.4. CONCLUSION

A simple but efficient and environmentally benign methodology for synthesis of β- amino alcohols from aromatic amines and alkylene carbonates using highly active and reusable solid base Na-Y catalyst have been demonstrated. Excellent yields of chiral β-amino alcohols were obtained (> 95%) from chiral alkylene carbonate by using this methodology. It has also been shown that alkylene carbonates have excellent reactivity and at the same time they are nontoxic and safer to work with and can effectively replace the use of epoxides in synthesis β-amino alcohols.

In this work, tandem synthesis of β-amino alcohols from aniline, dialkyl carbonate and ethylene glycol was also demonstrated for the first time. The route comprises of tandem synthesis of β-amino alcohol involving in-situ transesterification reaction of dialkyl carbonate by ethylene glycol to ethylene carbonate followed by *N*-alkylation of aniline by ethylene carbonate. This reaction system was investigated in high-pressure as well as in pot reaction conditions. Various process parameters were investigated for the reaction of aniline, dimethyl carbonate and ethylene glycol under high-pressure reaction condition, it was observed that selectivity of mono β-amino alcohol i.e. *N*-phenyl ethanolamine was very poor (55%). The selectivity of *N*-phenyl ethanolamine was decreased due to the more formation of *N*-methyl *N*-phenyl ethanolamine by *N*-methylation of *N*-phenyl ethanolamine in presence of DMC under high pressure condition. The selectivity of mono β-amino alcohol was improved drastically (91-99%) by carrying out the reaction under pot reaction conditions using diethyl carbonate or dibutyl carbonate. It was observed that Na-Y catalyst was highly effective in converting various anilines to β-amino alcohols in high yield with good

catalyst recyclability. Reactivity of various aromatic anilines and organic carbonates was studied and it was observed that electron-donating substituents enhanced the nucleophilicity of aniline thus increasing the reactivity as well as yield of β-amino alcohols, while electron-withdrawing substituents on the aniline ring decreased the reactivity as well as yield of β-amino alcohol. Diethyl carbonate was found most suitable transesterification agent for tandem synthesis of β-amino alcohol as it was not good *N*-alkylating agent, thus selectively β-amino alcohols were formed. Dimethyl carbonate was highly reactive which gave more *N*-methylated products that decreased the selectivity of β-amino alcohol whereas dibutyl carbonate was less reactive for transesterification reaction that resulted in poor yield of β-amino alcohol. It has also been shown that by manipulating process parameters, it is possible to maximize the yield of either mono amino alcohol or methylated amino alcohol or bis amino alcohols.

4.5. IDENTIFICATION OF β-AMINO ALCOHOLS

_N_-phenyl ethanolamine (3)[33]

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.86 (brs, 2H; NH & OH); 3.27 (t, *J* = 5.4 Hz, 2H; -NCH_2-); 3.80 (t, *J* = 5.4 Hz, 2H; -OCH_2-); 6.63-6.77 (m, 3H; -CH, Ar); 7.14-7.22 (m, 2H; -CH, Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 45.99 (-NCH_2); 60.97 (-OCH_2); 113.20 (-CH, Ar); 117.84 (-CH, Ar); 129.21 (-CH, Ar); 148.00 (-C, Ar). IR (film): ν_{max} = 3392 (OH, NH), 2943 (CH), 1602 (C=C, Ar), 1506 (C=C, Ar), 1323 (C-N, Ar), 1058, 752 cm^{-1}. GC-MS (70 eV, EI): m/z (%): 137 (23) $[M]^+$, 106 (100) $[C_6H_5NH{=}CH_2]^+$, 91 (2), 77 (23), 65 (3), 51 (8).

2-[(4-methylphenyl) amino] ethanol (3a)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.24 (s, 3H; -CH_3-Ar); 2.59 (brs, 2H; NH & OH); 3.27 (t, *J* = 5.4 Hz, 2H; -NCH_2-); 3.80 (t, *J* = 5.4 Hz, 2H; -OCH_2-); 6.57 (d, *J* = 8.5 Hz, 2H; -CH, Ar); 6.98 (d, *J* = 8.5 Hz, 2H; -CH, Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.32 (-

CH_3, Ar); 46.57 (-NCH_2); 61.10 (-OCH_2); 113.58 (-CH, Ar); 127.32 (-C, Ar); 129.73 (-CH, Ar); 145.63 (-C, Ar). IR (film): ν_{max} = 3382 (OH, NH), 2918 (CH), 1616 (C=C, Ar), 1519 (C=C, Ar), 1319 (C-N, Ar), 1062, 810 cm^{-1}. GC-MS (70 eV, EI) *m/z* (%): 151 (24) $[M]^+$, 120 (100) $[p\text{-}CH_3\text{-}C_6H_4NH{=}CH_2]^+$, 106 (3), 91 (17), 77 (6), 65 (7), 51 (2).

2-[(4-methoxylphenyl) amino] ethanol (3b)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.04 (brs, 2H; NH & OH); 3.23 (t, *J* = 5.3 Hz, 2H; -NCH_2-); 3.73 (s, 3H; -OCH_3-Ar); 3.80 (t, *J* = 5.3 Hz, 2H; -OCH_2-); 6.64 (d, *J* = 9.1 Hz, 2H; -CH, Ar); 6.76 (d, *J* = 9.1 Hz, 2H; -CH, Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 47.84 (-NCH_2); 55.64 (-OCH_3, Ar); 60.53 (-OCH_2); 114.81 (-CH, Ar); 115.61 (-CH, Ar); 140.83 (-C, Ar); 153.06 (-C, Ar). IR (film): ν_{max} = 3421 (OH, NH), 2945 (CH), 1624 (C=C, Ar), 1514 (C=C, Ar), 1305 (C-N, Ar), 1076, 833 cm^{-1}. GC-MS (70 eV, EI) *m/z* (%): 167 (23) $[M]^+$, 136 (100) $[p\text{-}OCH_3\text{-}C_6H_4NH{=}CH_2]^+$, 121 (11), 108 (11), 93 (4), 77 (4), 65 (3).

2-[(4-aminophenyl) amino] ethanol (3c)

^{1}H NMR (200 MHz, Acetone-d_6): δ = 2.95 (brs, 4H; 3NH & OH); 3.19 (t, *J* = 5.6 Hz, 2H; -NCH_2-); 3.72 (t, *J* = 5.6 Hz, 2H; -OCH_2-); 6.47 (d, *J* = 8.7 Hz, 2H; -CH, Ar); 6.60 (d, *J* = 8.7 Hz, 2H; -CH, Ar). ^{13}C NMR (100 MHz, Acetone-d_6): δ = 47.18 (-NCH_2); 61.04 (-OCH_2); 113.72 (-CH, Ar); 121.64 (-CH, Ar); 142.07 (-C, Ar); 146.09 (-C, Ar). IR (film): ν_{max} = 3363 (OH, NH), 2945 (CH), 1614 (C=C, Ar), 1519 (C=C, Ar), 1325 (C-N, Ar), 1058, 827 cm^{-1}. GC-MS (70 eV, EI) *m/z* (%): 152 (36) $[M]^+$, 121 (100) $[p\text{-}NH_2\text{-}C_6H_4NH{=}CH_2]^+$, 107 (5), 93 (23), 77 (6), 65 (11), 52 (3).

3-[(2-hydroxyethyl) amino] phenol (3d)

^{1}H NMR (200 MHz, Acetone-d_6): δ = 2.96 (brs, 2H; NH & OH); 3.19 (t, *J* = 5.6 Hz, 2H; -NCH_2-); 3.72 (t, *J* = 5.6 Hz, 2H; -OCH_2-); 4.77 (brs, 1H; OH,Ar); 6.08 - 6.17 (m, 3H; -CH, Ar); 6.90 (dd, *J* = 7.8 & 8.5 Hz, 1H; -CH, Ar) ^{13}C NMR (100 MHz, Acetone-d_6): δ = 46.75 (-NCH_2); 61.20 (-OCH_2); 100.33 (-CH, Ar); 104.64 (-CH, Ar); 105.37 (-CH, Ar); 130.43 (-CH, Ar); 151.33 (-C, Ar); 159.17 (-C, Ar). IR (film): ν_{max} = 3332 (OH, NH), 2947 (CH), 1606 (C=C, Ar), 1496 (C=C, Ar), 1338 (C-N, Ar), 1055, 767 cm^{-1}. GC-MS (70 eV, EI) *m/z* (%): 153 (34) $[M]^+$, 122 (100) $[m\text{-}OH\text{-}C_6H_4NH{=}CH_2]^+$, 109 (3), 94 (13), 77 (5), 65 (9), 53 (2).

2-[(4-chlorophenyl) amino] ethanol (3e)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.56 (brs, 2H; NH & OH); 3.27 (t, *J* = 5.3 Hz, 2H; -NCH_2-); 3.83 (t, *J* = 5.3 Hz, 2H; -OCH_2-); 6.56 (d, *J* = 8.9 Hz, 2H; -CH, Ar); 7.1 (d, *J* = 8.9 Hz, 2H; -CH, Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 46.10 (-NCH_2); 60.96 (-OCH_2); 114.27 (-CH, Ar); 122.41 (-C, Ar); 129.04 (-CH, Ar); 146.55 (-C, Ar). IR (KBr): ν_{max} = 3305 (OH), 3190 (NH), 2947 (CH), 1600 (C=C, Ar), 1499 (C=C, Ar), 1312 (C-N, Ar), 1063, 813 cm^{-1}. GC-MS (70 eV, EI) *m/z* (%): 171 (26) $[M]^+$, 140 (100) [*p*-Cl-$C_6H_4NH{=}CH_2]^+$, 111 (8), 105 (9), 91 (2), 77 (10), 65 (2).

2-[(4-nitrophenyl) amino] ethanol (3f)

^{1}H NMR (200 MHz, Acetone-d_6): δ = 2.83 (brs, 2H; NH & OH); 3.38 (t, *J* = 5.4 Hz, 2H; -NCH_2-); 3.77 (t, *J* = 5.4 Hz, 2H; -OCH_2-); 6.73 (d, *J* = 9.2 Hz, 2H; -CH, Ar); 8.01 (d, *J* = 9.2 Hz, 2H; -CH, Ar). ^{13}C NMR (50 MHz, Acetone-d_6): δ = 46.23 (-NCH_2); 60.83 (-OCH_2); 111.76 (-CH, Ar); 126.79 (-CH, Ar); 137.82 (-C, Ar); 155.48 (-C, Ar). IR (KBr): ν_{max} = 3442 (OH), 3274 (NH), 2968 (CH), 1599 (C=C, Ar), 1503 (C=C, Ar), 1327 (C-N, Ar), 1040, 753 cm^{-1}. GC-MS (70 eV, EI) *m/z* (%): 182 (23) $[M]^+$, 151 (100) [*p*-NO_2-$C_6H_4NH{=}CH_2]^+$, 135 (5), 105 (58), 93 (2), 76 (7), 65 (4), 50 (4).

***N*-phenyl diethanolamine (4)**

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.49 (t, *J* = 4.9 Hz, 4H; -NCH_2-); 3.75 (t, *J* = 4.9 Hz, 4H; -OCH_2-); 6.63-6.75 (m, 3H; -CH, Ar); 7.17-7.25 (m, 2H; -CH, Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.21 (-NCH_2); 60.48 (-OCH_2); 112.41 (-CH, Ar); 116.75 (-CH, Ar); 129.20 (-CH, Ar); 147.62 (-C, Ar). IR (film): ν_{max} = 3382 (OH, NH), 2952 (CH), 1598 (C=C, Ar), 1504 (C=C, Ar), 1355 (C-N, Ar), 1062, 750 cm^{-1}. GC-MS (70 eV EI) m/z (%): 181 (16) $[M]^+$, 150 (100) $[C_6H_5N(C_2H_4OH){=}CH_2]^+$, 106 (56) , 91 (7), 77 (16) , 65 (1), 52 (4), 45 (7).

***N*-methyl *N*-phenyl ethanolamine (7)**

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.74 (brs, 1H; OH); 2.96 (s, 3H; -NCH_3-); 3.47 (t, *J* = 5.6 Hz, 2H; -NCH_2-); 3.81 (t, *J* = 5.6 Hz, 2H; -OCH_2-); 6.72-6.83 (m, 3H; -CH, Ar); 7.21-7.29 (m, 2H; -CH, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.68 (-NCH_3); 55.32 (-NCH_2); 59.90 (-OCH_2); 112.93 (-CH, Ar); 117.07 (-CH, Ar); 129.11 (-CH, Ar); 149.94 (-C, Ar). IR (film): ν_{max} = 3344 (OH, NH), 2906 (CH), 1596 (C=C, Ar), 1505 (C=C, Ar),

1340 (C-N, Ar), 1056, 746 Cm^{-1}. GC-MS (70 eV, EI) *m/z* (%): 151 (17) $[M]^+$,120 (100) $[C_6H_5N(CH_3)=CH_2]^+$, 105 (11), 91 (5), 77 (15) , 65 (1), 51 (5).

(2R)-1-(phenyl amino) propan-2-ol[34] (**13a**, 96% pure containing 4% **14a**)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.3 Hz, 3H; -CH_3); 2.64 (brs, 2H; NH & OH); 2.98 (dd, *J* = 8.4 & 12.8 Hz, 1H; -NCH-); 3.21 (dd, *J* = 3.4 & 12.8 Hz, 1H; -NCH); 3.95-4.09 (m, 1H; -OCH-); 6.64 - 6.67 (m, 3H; -CH, Ar); 7.15 – 7.25 (m, 2H; -CH, Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.74 (-CH_3); 51.59 (-NCH_2); 66.28 (-OCH_2); 113.21 (-CH, Ar); 117.83 (-CH, Ar); 129.23 (-CH, Ar); 148.12 (-C, Ar). IR (film): ν_{max} = 3394 (OH, NH), 2970 (CH), 1602 (C=C, Ar), 1506 (C=C, Ar), 1319 (C-N, Ar), 1072, 750 cm^{-1}. GC-MS (70 eV, EI) *m/z* (%): 151 (21) $[M]^+$, 106 (100) $[C_6H_5NH=CH_2]^+$, 93 (2), 77 (16), 65 (2), 51 (5). Chiral HPLC: (Dicel chiral OD-H column; hexane:*i*-PrOH 97.5:2.5%, V/V, flow rate, 1 ml/min); t_1= 41.12 min; **14a**(minor), t_2= 44.62 min; **13a (**major**)**; t_4= 59.31 min; **14b**.

(2S)-1-(phenyl amino) propan-2-ol[34] (**13b**, 96% pure containing 4% **14b**)

Chiral HPLC: (Dicel chiral OD-H column; hexane:*i*-PrOH 97.5:2.5%, V/V, flow rate, 1 ml/min); t_1= 41.69 min; **14a**(minor), t_2= 44.72 min; **13a (**minor**)**; t_3= 57.48 min; **13b (**major**)**; Other spectral data is same as compound **13a**.

2-phenylamino 1-phenyl ethanol (10b)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.61 (brs, 2H; NH & OH); 3.32 (dd, *J* = 8.5 & 13.1 Hz,1H; -NCH_2-); 3.48 (dd, *J* = 4.0 & 13.1 Hz, 1H; -NCH_2); 4.96 (dd, *J* = 4.0 & 8.5 Hz, 1H; -OCH-); 6.68 (d, *J* = 7.6 Hz, 2H, CH, Ar); 6.76 (t, *J* = 7.3 Hz, 1H; -CH, Ar); 7.20 (t, *J* = 7.5 Hz, 2H; -CH, Ar); 7.30-7.42 (m, 5H; -CH, Ar). IR (in $CHCl_3$): ν_{max} = 3610 (OH), 3433 (NH), 2927 (CH), 1604 (C=C, Ar), 1505 (C=C, Ar), 1316 (C-N, Ar), 1060, 790 cm^{-1}. GC-MS (70 eV, EI) *m/z* (%): 213 (8) $[M]^+$, 194 (13), 182 (10), 165 (2), 106 (100) $[C_6H_5NH=CH_2]^+$, 91 (7), 77 (33), 65 (3), 51 (9).

2-phenylamino-2-phenyl ethanol (11b)[1b,25]

^{1}H NMR (200 MHz, $CDCl_3$):δ = 2.71 (brs, 2H; NH & OH); 3.76 (dd, *J* = 7.0 & 11.1 Hz, 1H; -OCH_2-); 3.96 (dd, *J* = 4.2 & 11.1 Hz, 1H; -OCH_2-); 4.50 (dd, *J* = 4.2 & 7.0 Hz, 1H; -NCH-) 6.55 (d, *J* = 7.5 Hz, 2H, -CH, Ar); 6.88 (t, *J* = 7.3 Hz, 1H; -CH, Ar); 7.11 (t, J = 7.4 Hz, 2H; -CH, Ar); 7.30-7.36 (m, 5H; -CH, Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ =

59.83 (-NCH); 67.33 (-OCH_2); 113.82 (-CH, Ar); 117.86 (-CH, Ar); 126.70 (-CH, Ar); 127.58 (-CH, Ar); 128.80 (-CH, Ar); 129.13 (-CH, Ar); 140.10 (-C, Ar); 147.20 (-C, Ar). IR (film): ν_{max} = 3396 (OH, NH), 2927 (CH), 1602 (C=C, Ar), 1504 (C=C, Ar), 1317 (C-N, Ar), 1066, 750 cm^{-1}. GC-MS (70 eV, EI) *m/z* (%): 213 (7) $[M]^+$, 182 (100) $[C_6H_5NH{=}CHPh]^+$, 104 (17), 91 (4), 77 (23), 65 (2), 51 (5).

3-(phenylamino) propan-1-ol (12)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.87 (quint, *J* = 5.9 & 6.4 Hz, 2H,-CH_2-); 2.79 (brs; 2H, NH & OH); 3.27 (t, *J* = 6.4 Hz, 2H; -NCH_2-); 3.80 (t, *J* = 5.9 Hz, 2H; -OCH_2-); 6.62-6.76 (m, 3H; -CH, Ar); 7.14-7.22 (m, 2H; -CH, Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.85 (-CH_2); 41.89 (-NCH_2); 61.55 (-OCH_2); 113.10 (-CH, Ar); 117.63 (-CH, Ar); 129.22 (-CH, Ar); 148.28 (-C, Ar). IR (film): ν_{max} = 3381 (OH, NH), 2935 (CH), 1602 (C=C, Ar), 1506(C=C, Ar), 1321 (C-N, Ar), 1064, 752 cm^{-1}. GC-MS (70 eV EI) m/z (%): 151 (27) $[M]^+$, 132 (1), 118 (2), 106 (100) $[C_6H_5NH{=}CH_2]^+$, 93 (5), 77 (15), 65 (4), 51 (4).

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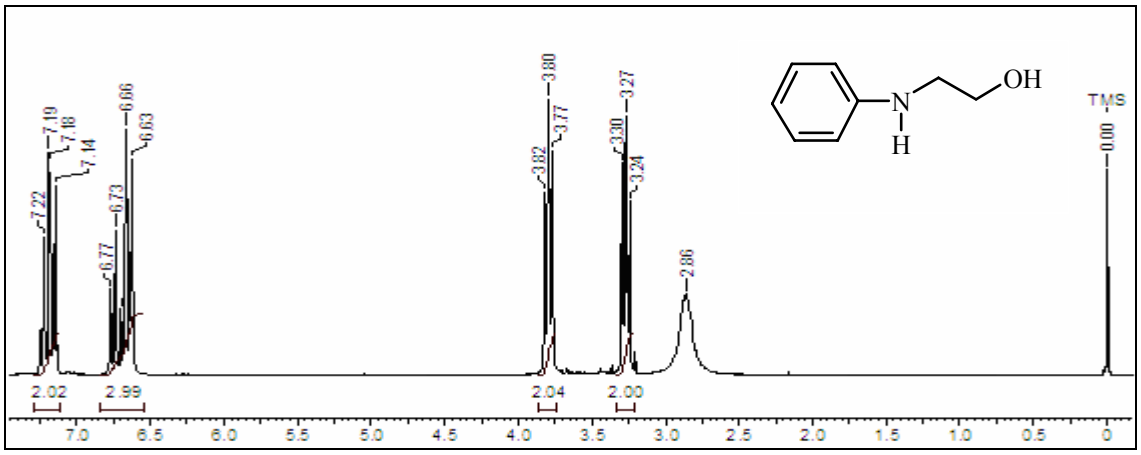
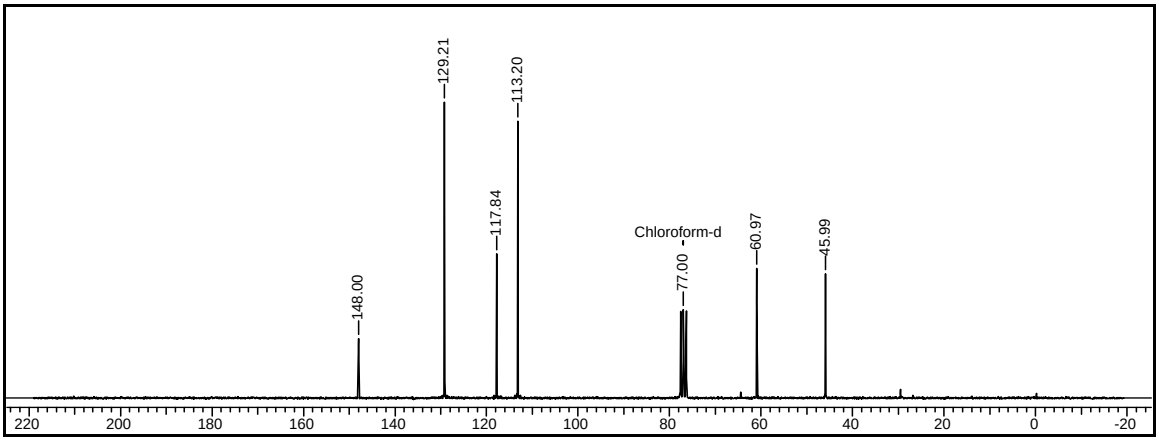
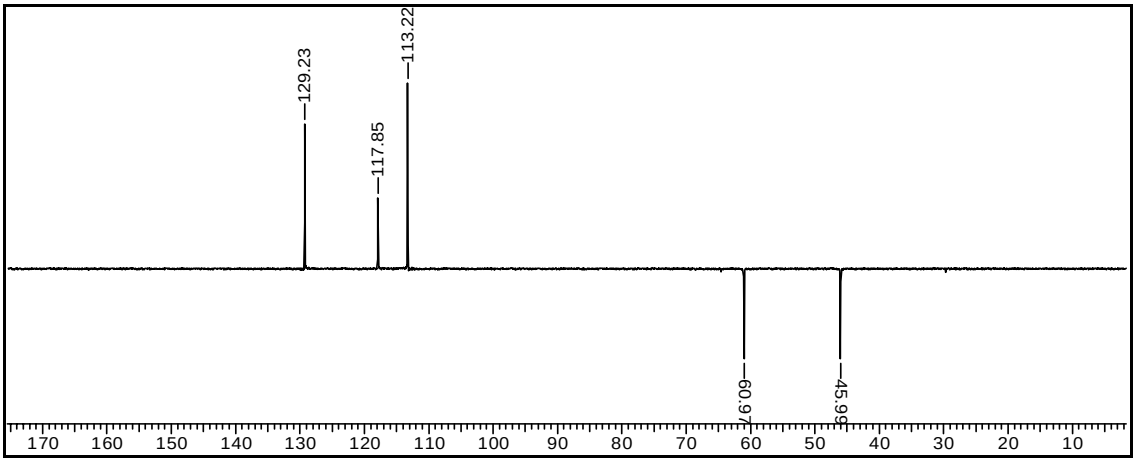
SPECTRA



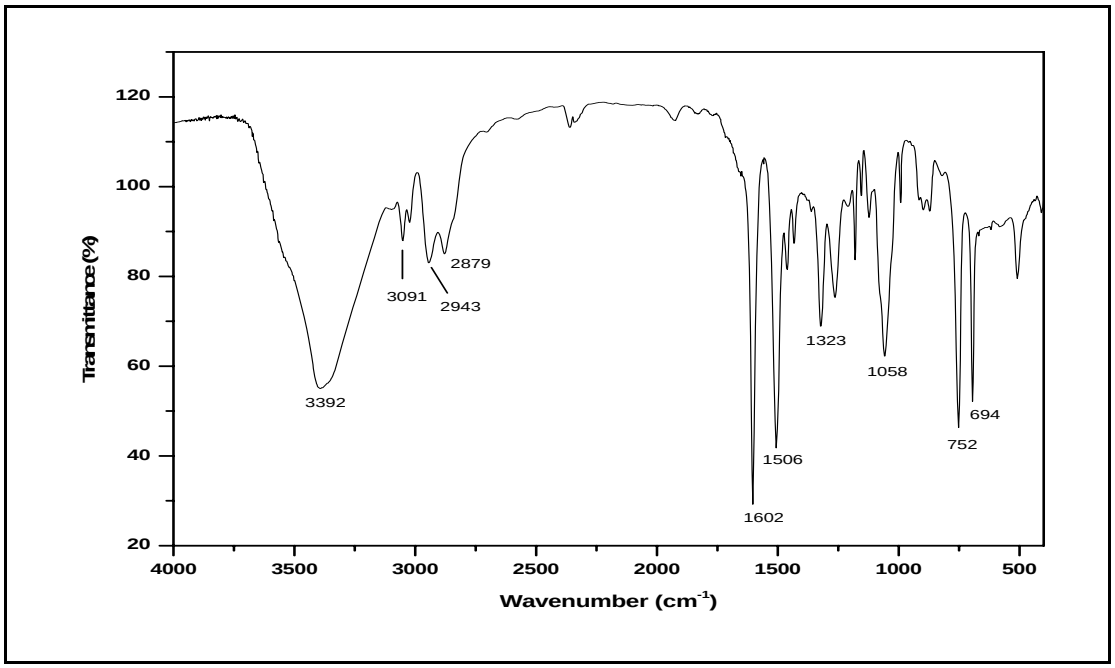
^{1}H NMR Spectrum of compound **3** ($CDCl_3$, 200 MHz)-NPEA



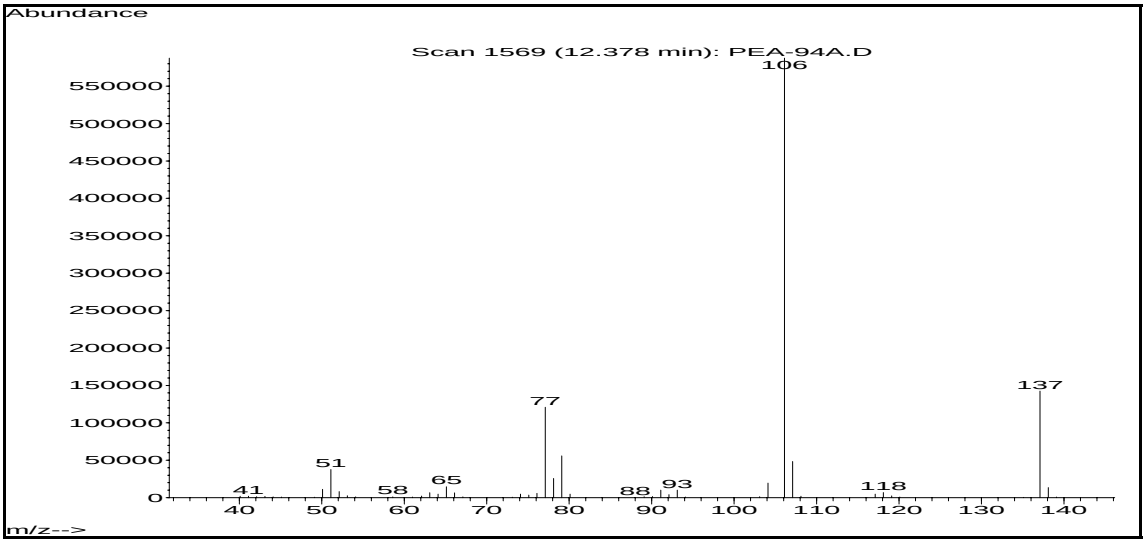
^{13}C NMR Spectrum of compound **3** ($CDCl_3$, 50 MHz)



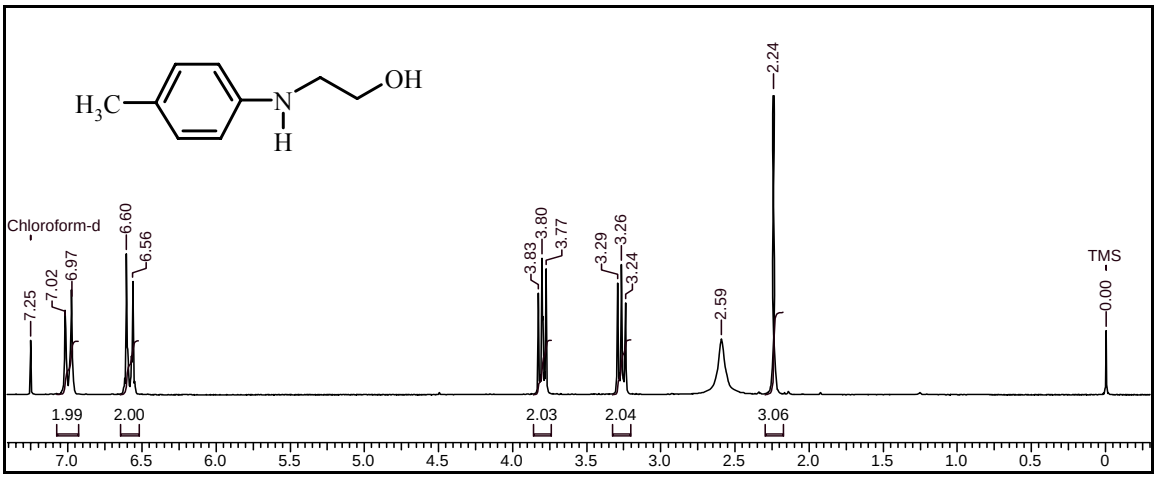
DEPT Spectrum of compound **3** ($CDCl_3$, 50 MHz)



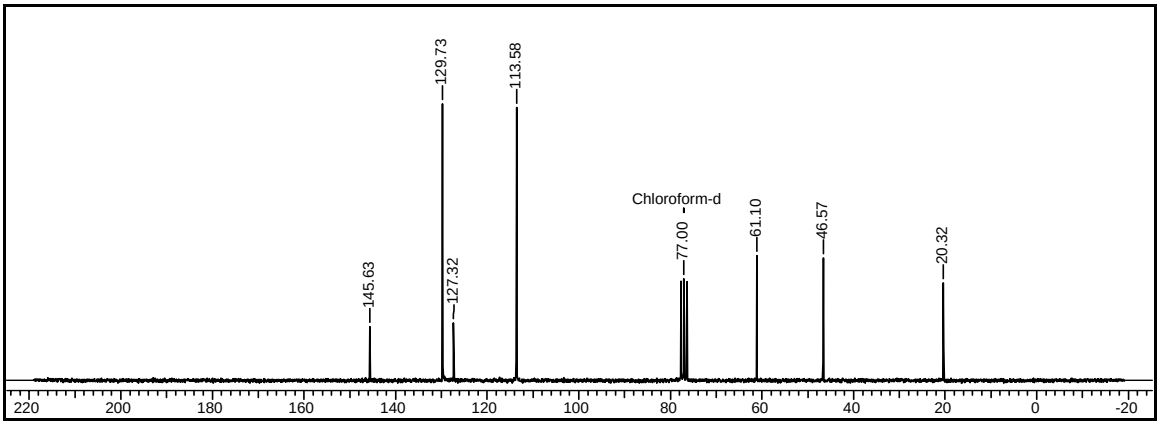
IR Spectrum of compound **3** (film)



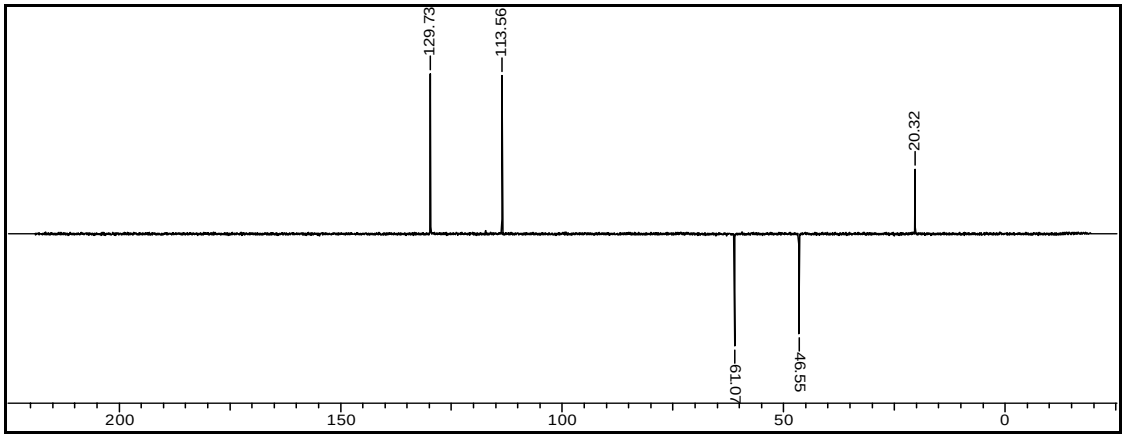
GC-MS Spectrum of compound **3** (70 eV, EI)



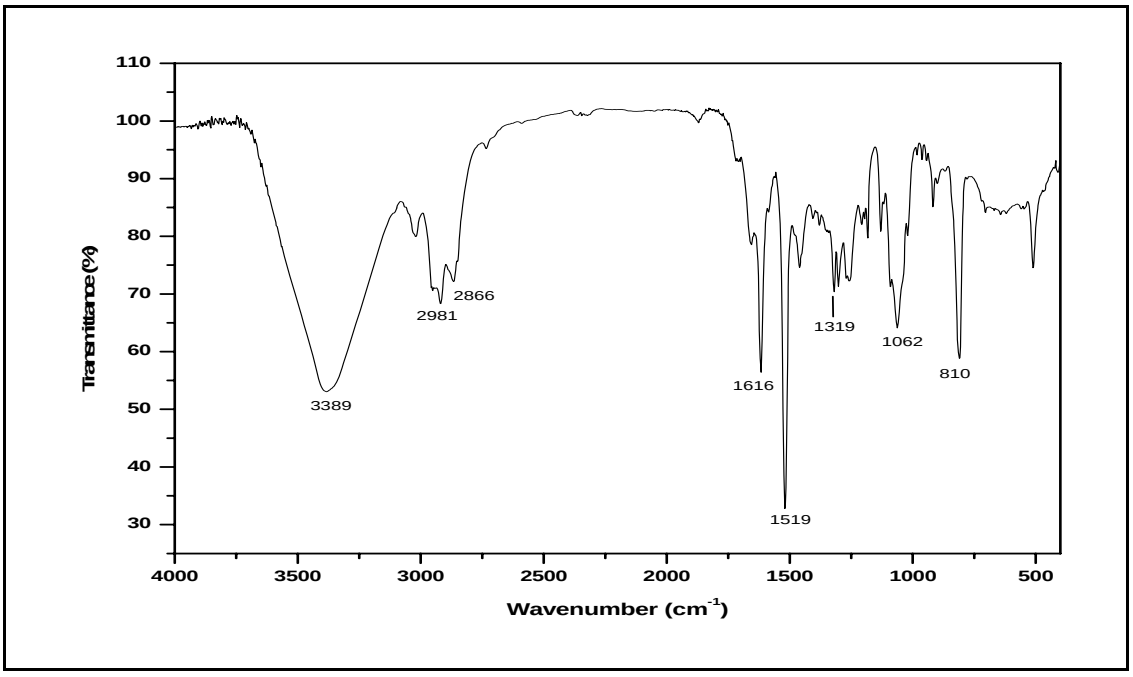
^{1}H NMR Spectrum of compound **3a** ($CDCl_3$, 200 MHz)



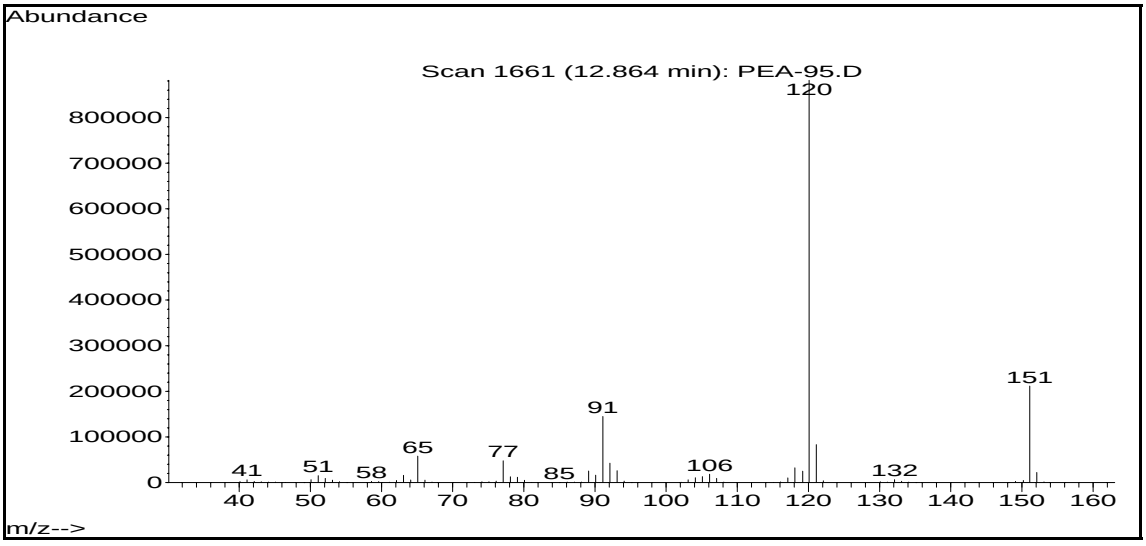
^{13}C NMR Spectrum of compound **3a** ($CDCl_3$, 50 MHz)



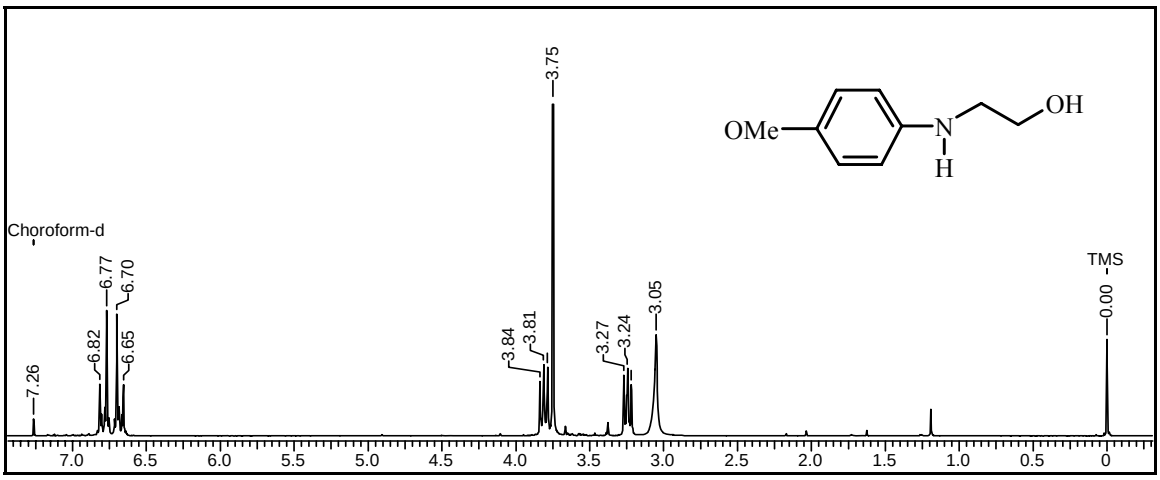
DEPT Spectrum of compound **3a** ($CDCl_3$, 50 MHz)



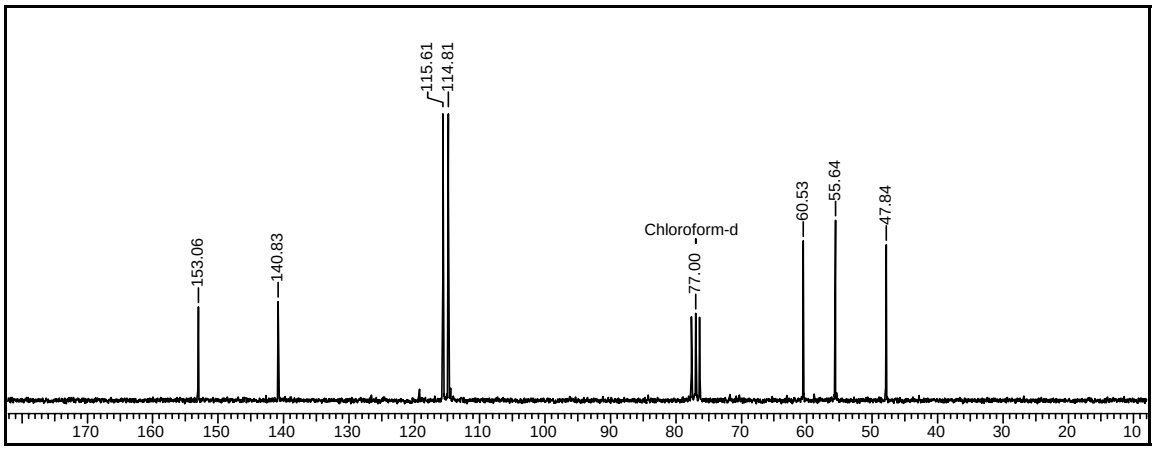
IR Spectrum of compound **3a** (film)



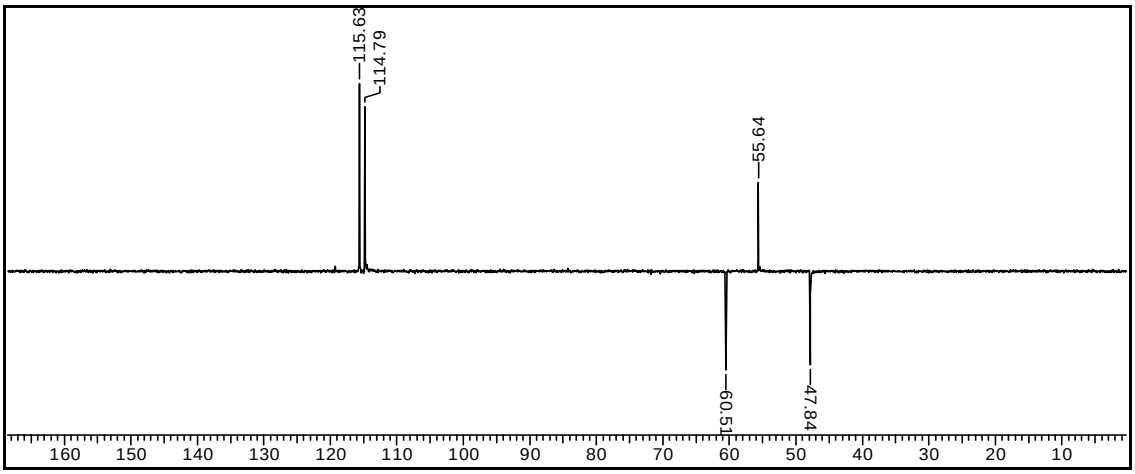
GC-MS Spectrum of compound **3a** (70 eV, EI)



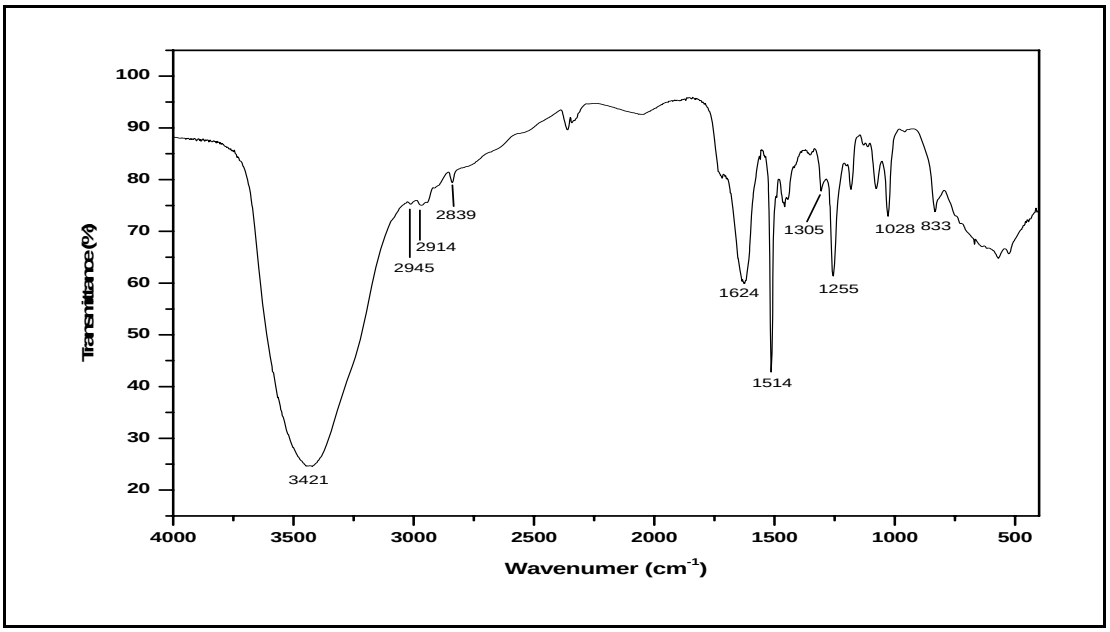
^{1}H NMR Spectrum of compound **3b** ($CDCl_3$, 200 MHz)



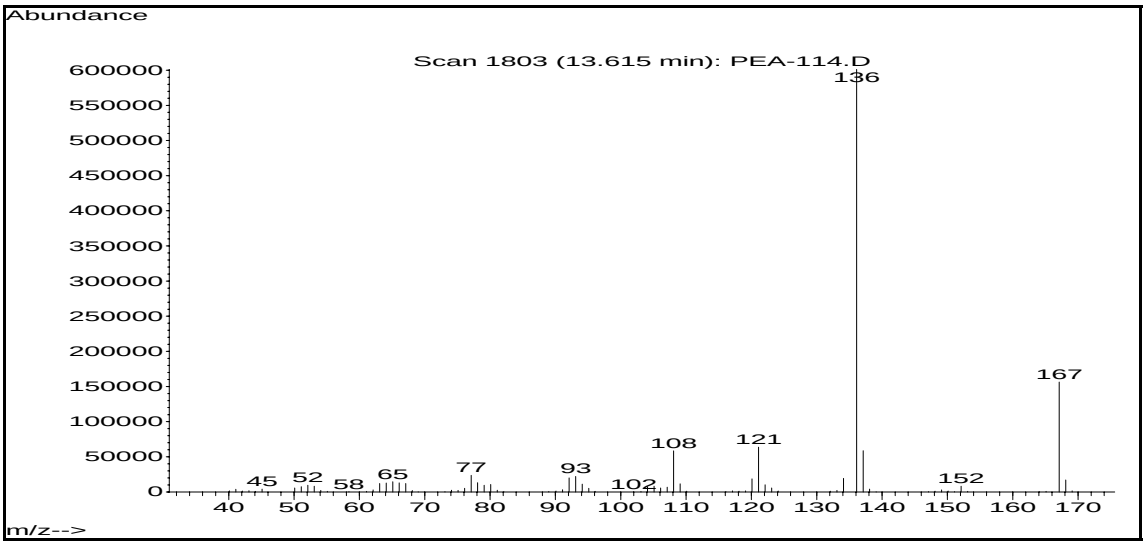
^{13}C NMR Spectrum of compound **3b** ($CDCl_3$, 50 MHz)



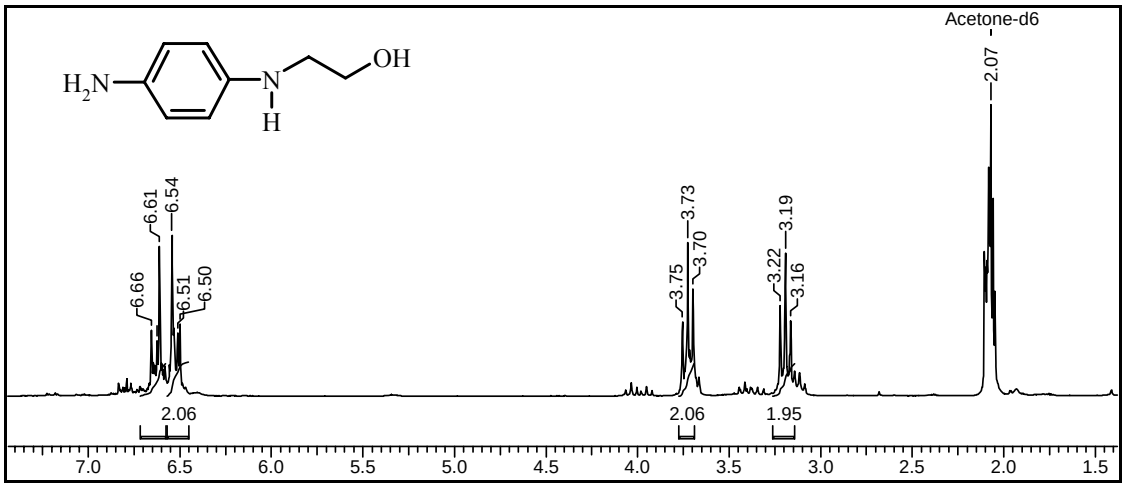
DEPT Spectrum of compound **3b** ($CDCl_3$, 50 MHz)



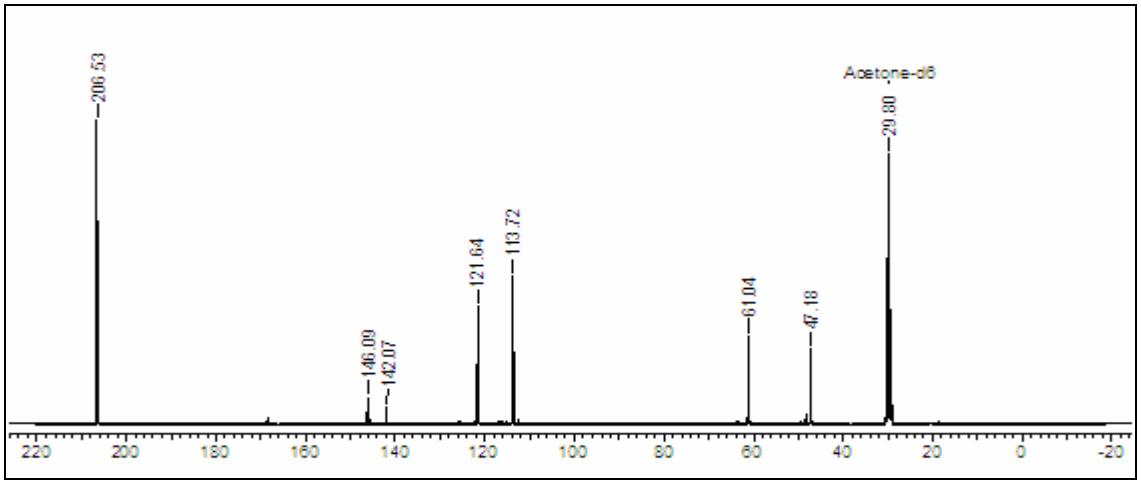
IR Spectrum of compound **3b** (film)



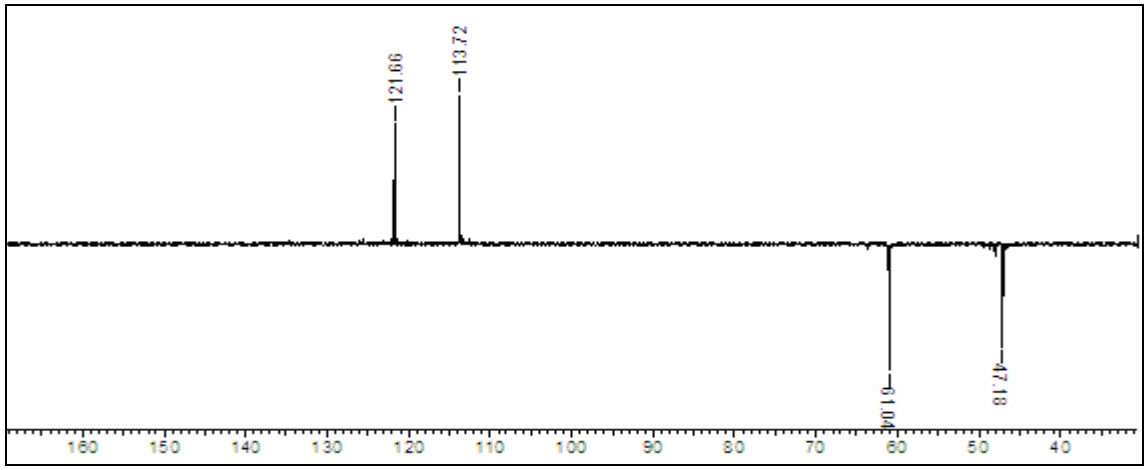
GC-MS Spectrum of compound **3b** (70 eV, EI)



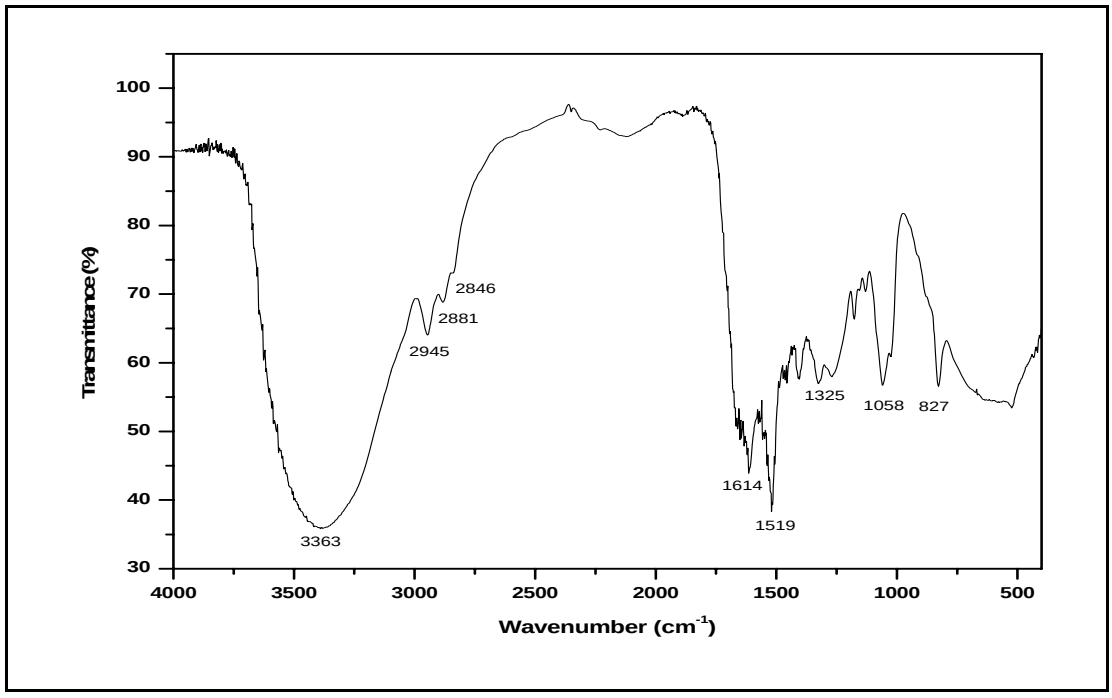
^{1}H NMR Spectrum of compound **3c** (Acetone-d_6, 200 MHz)



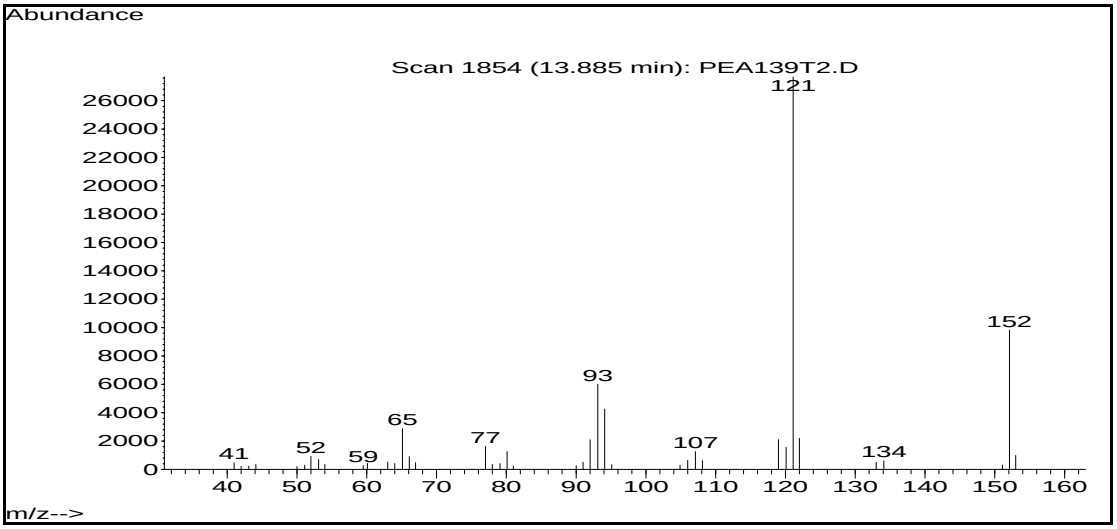
^{13}C NMR Spectrum of compound **3c** (Acetone-d_6, 100 MHz)



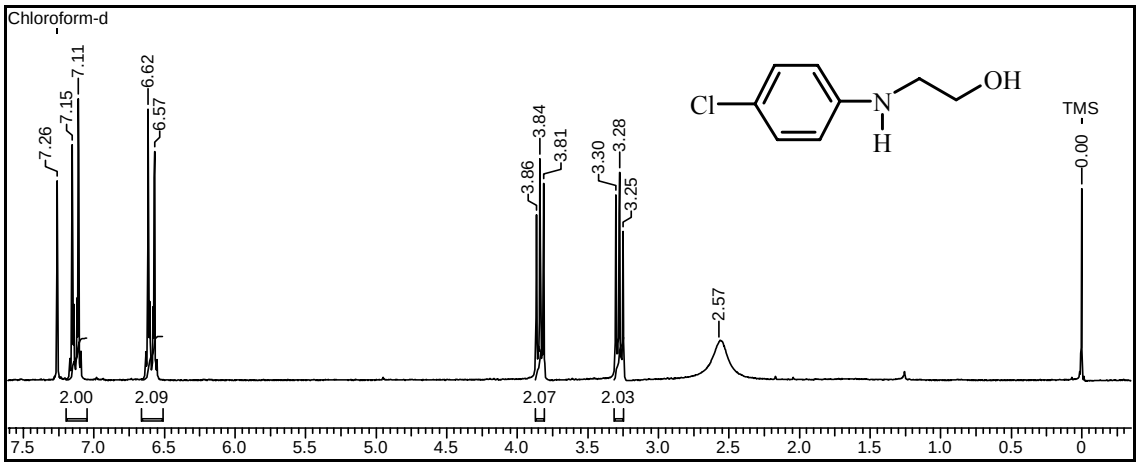
DEPT Spectrum of compound **3c** (Acetone-d_6, 100 MHz)



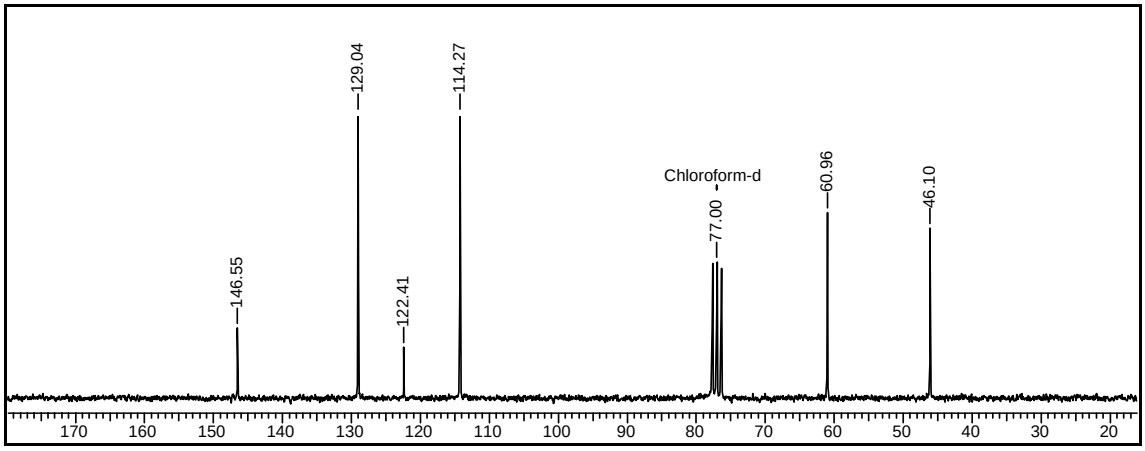
IR Spectrum of compound **3c** (film)



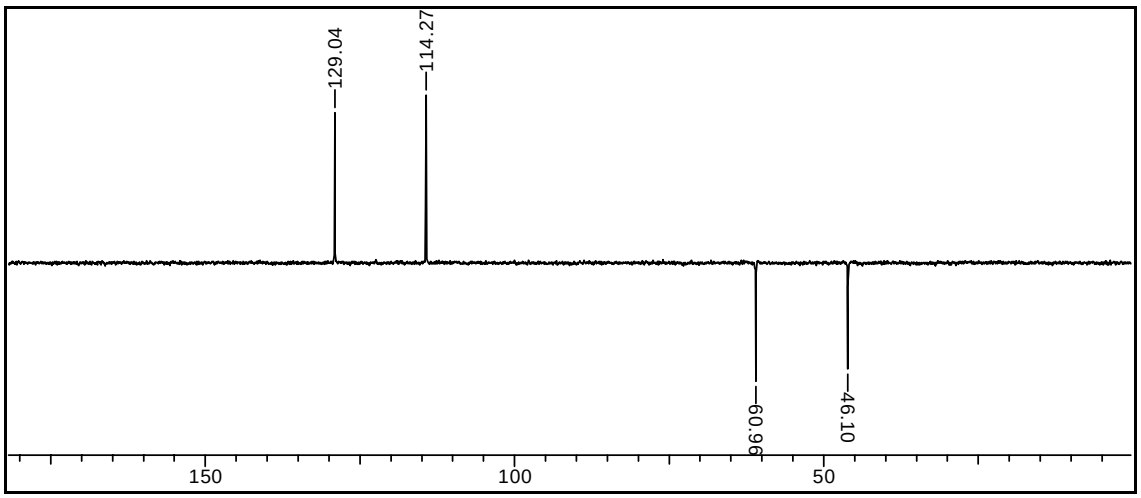
GC-MS Spectrum of compound **3c** (70 eV, EI)



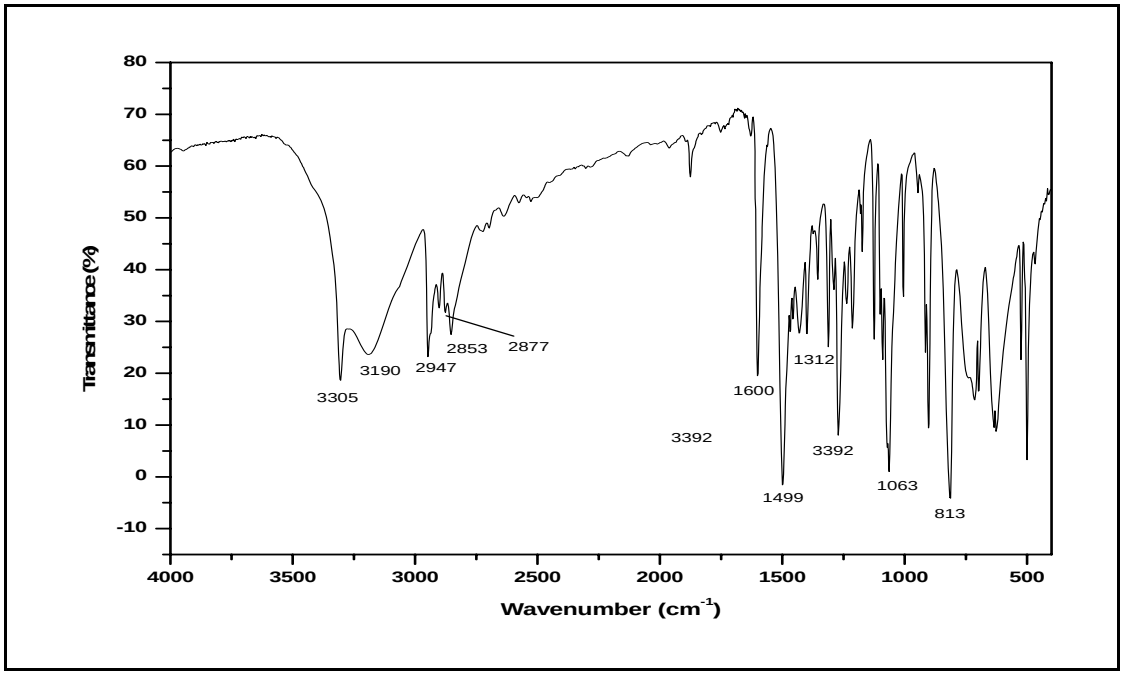
^{1}H NMR Spectrum of compound **3e** ($CDCl_3$, 200 MHz)



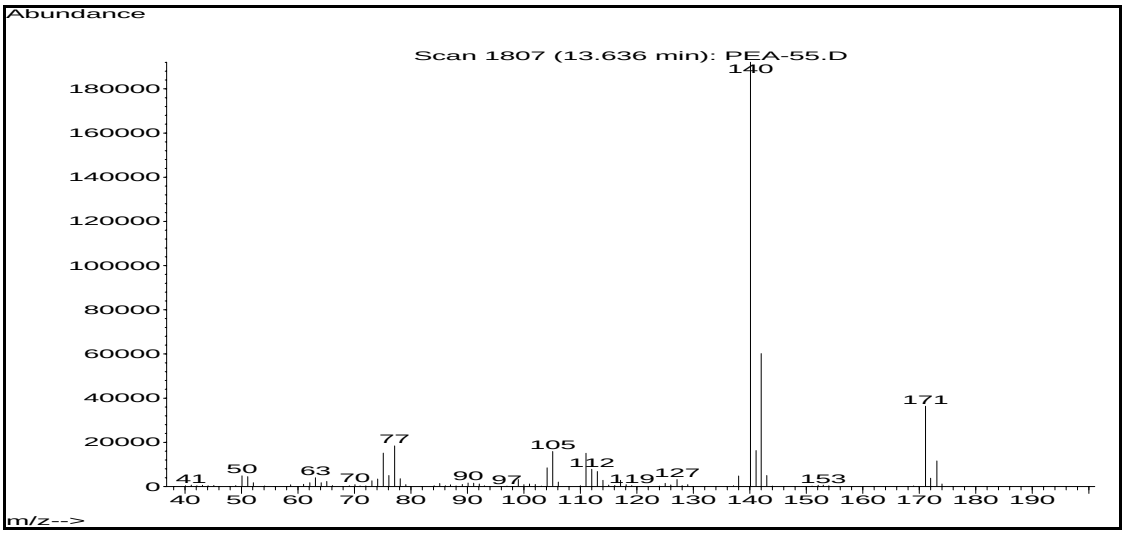
^{13}C NMR Spectrum of compound **3e** ($CDCl_3$, 50 MHz)



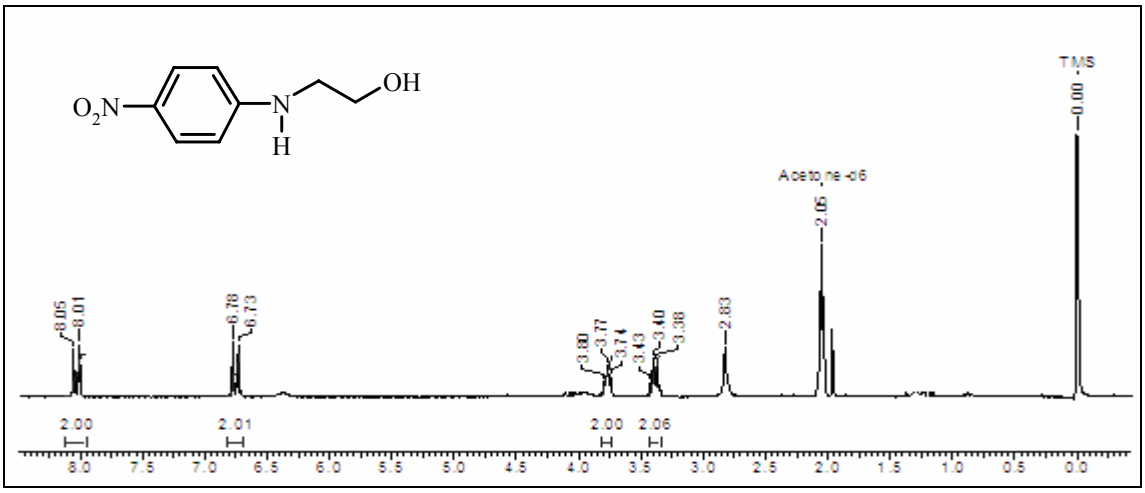
DEPT Spectrum of compound **3e** ($CDCl_3$, 50 MHz)



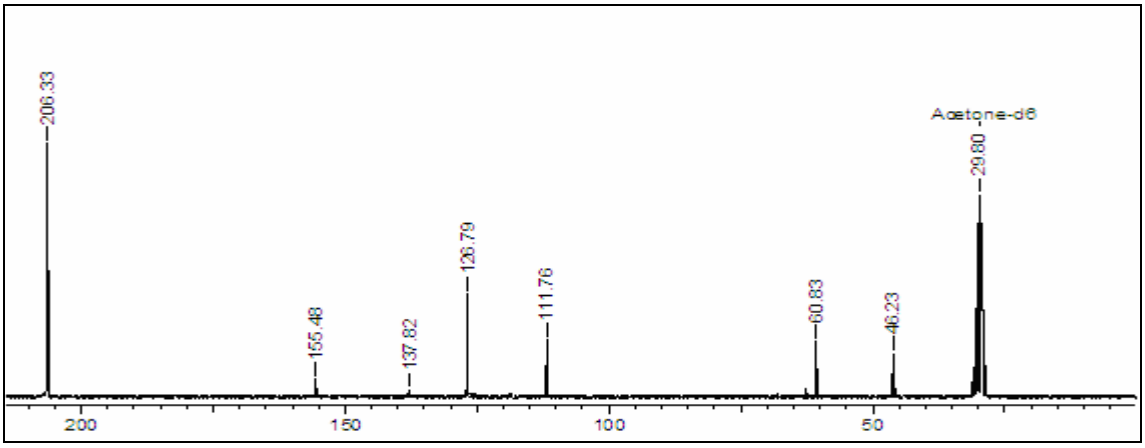
IR Spectrum of compound **3e** (KBr)



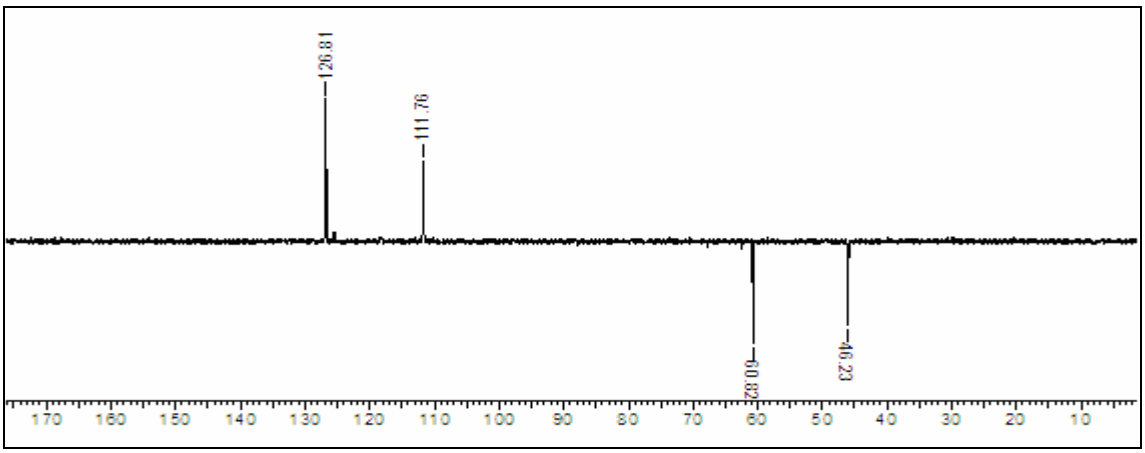
GC-MS Spectrum of compound **3e** (70 eV, EI)



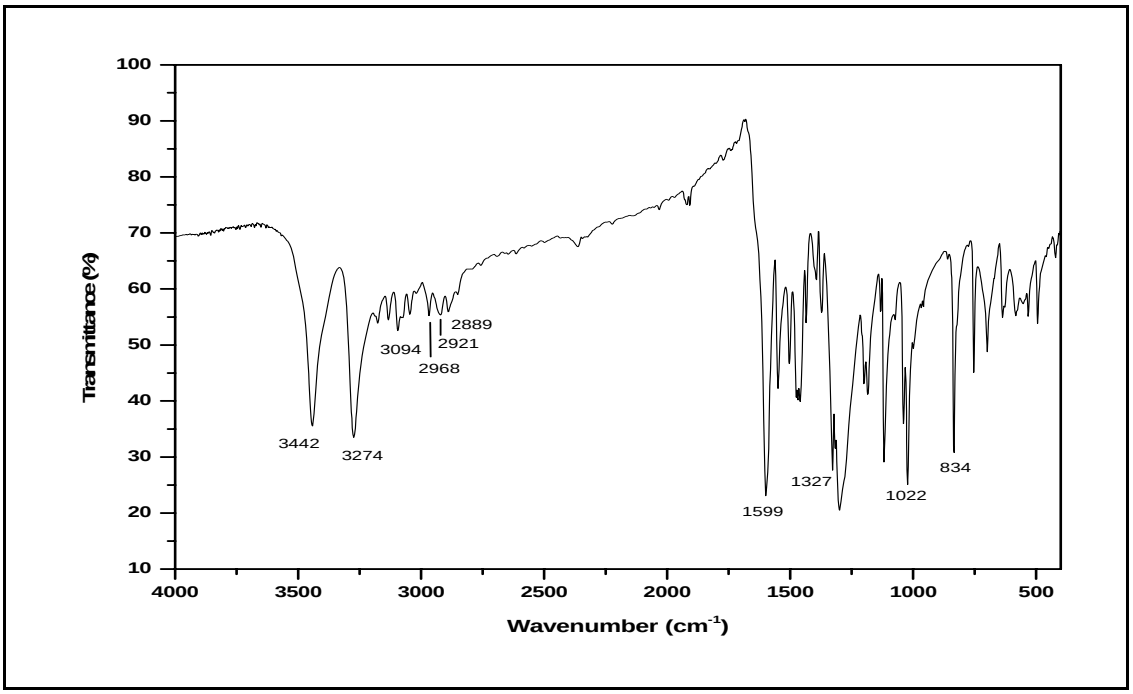
^{1}H NMR Spectrum of compound **3f** (Acetone-d_6, 200 MHz)



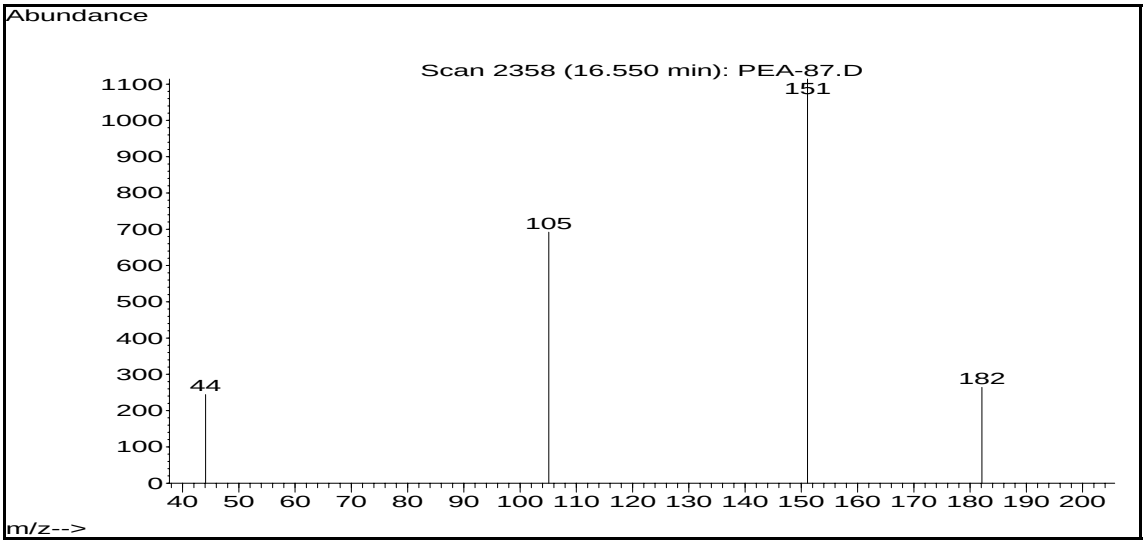
^{13}C NMR Spectrum of compound **3f** (Acetone-d_6, 50 MHz)



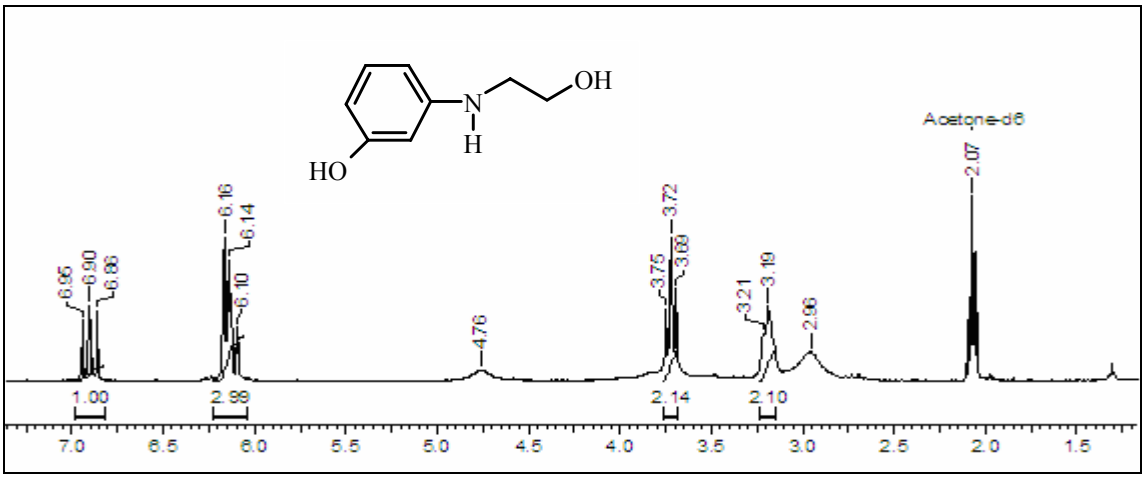
DEPT Spectrum of compound **3f** (Acetone-d_6, 50 MHz)



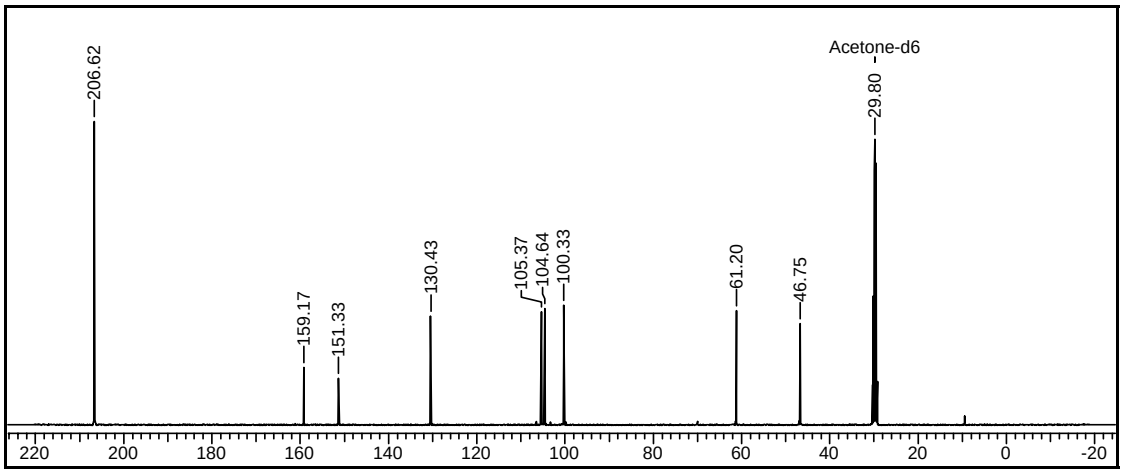
IR Spectrum of compound **3f** (KBr)



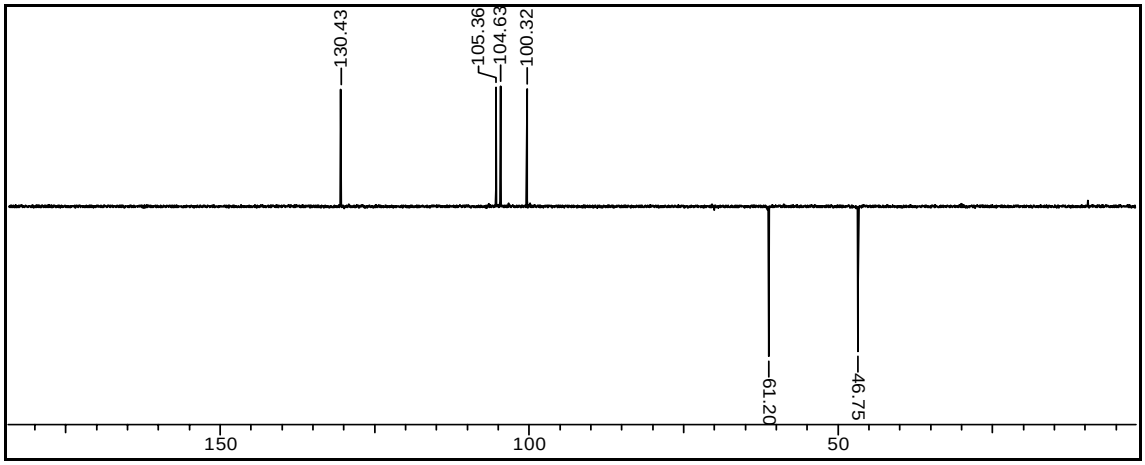
GC-MS Spectrum of compound **3f** (70 eV, EI)



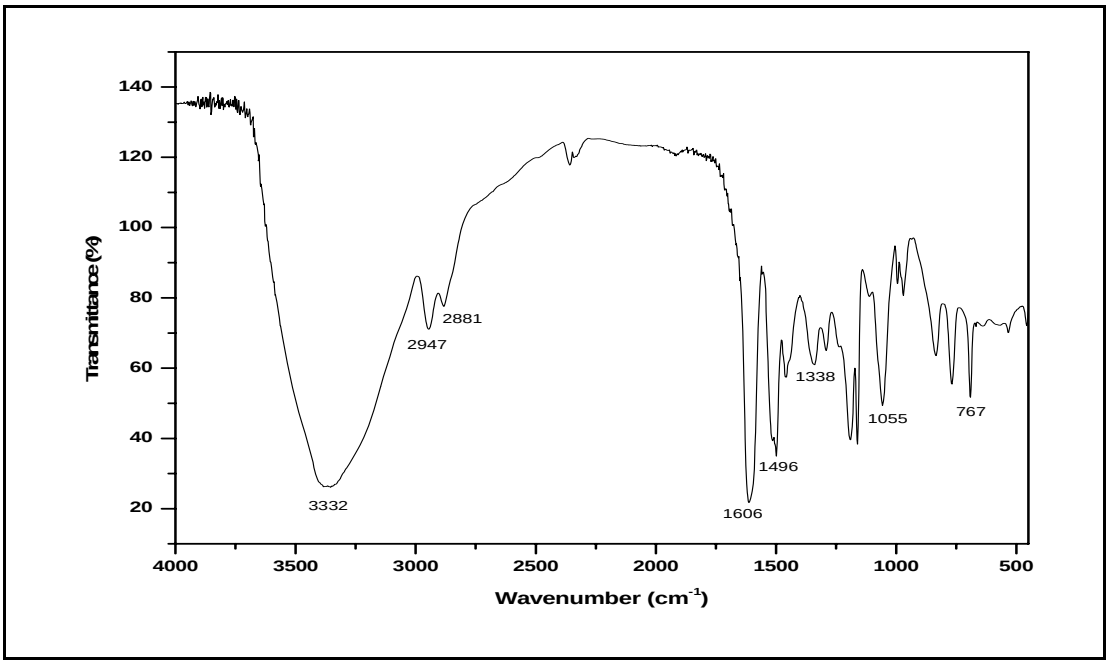
^{1}H NMR Spectrum of compound **3d** (Acetone-d_6, 200 MHz)



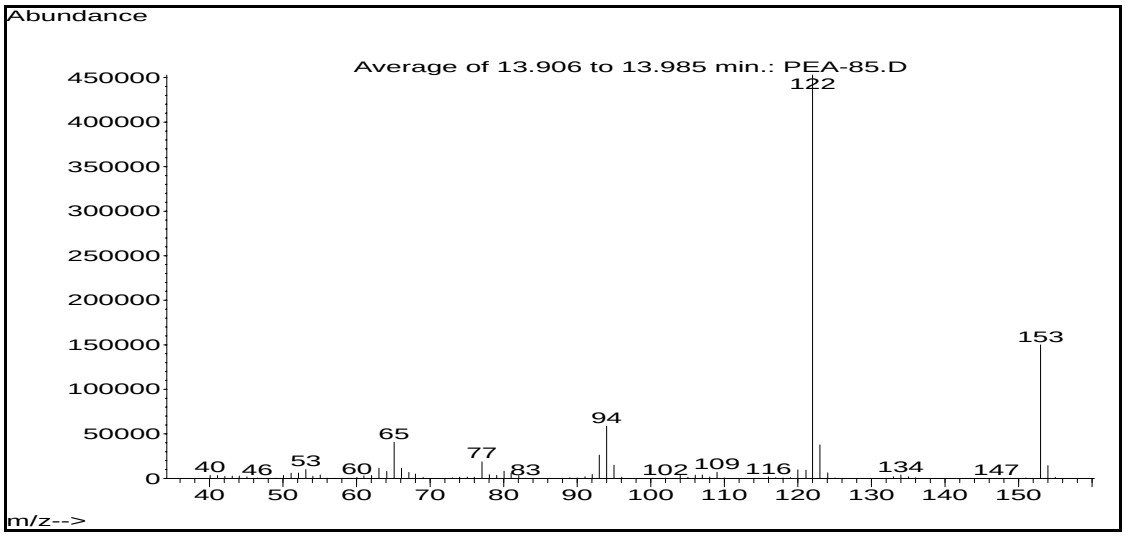
^{13}C NMR Spectrum of compound **3d** (Acetone-d_6, 100 MHz)



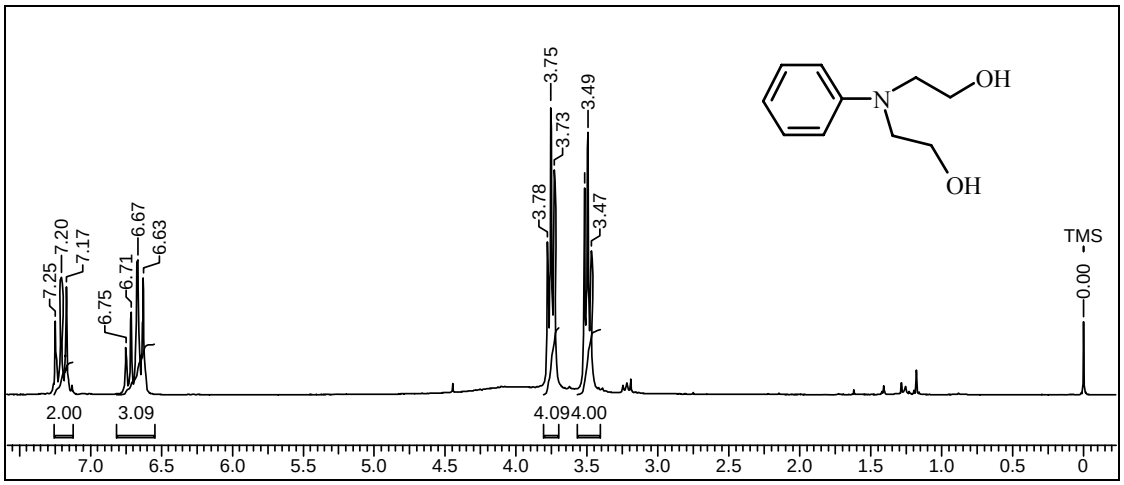
DEPT Spectrum of compound **3d** (Acetone-d_6, 100 MHz)



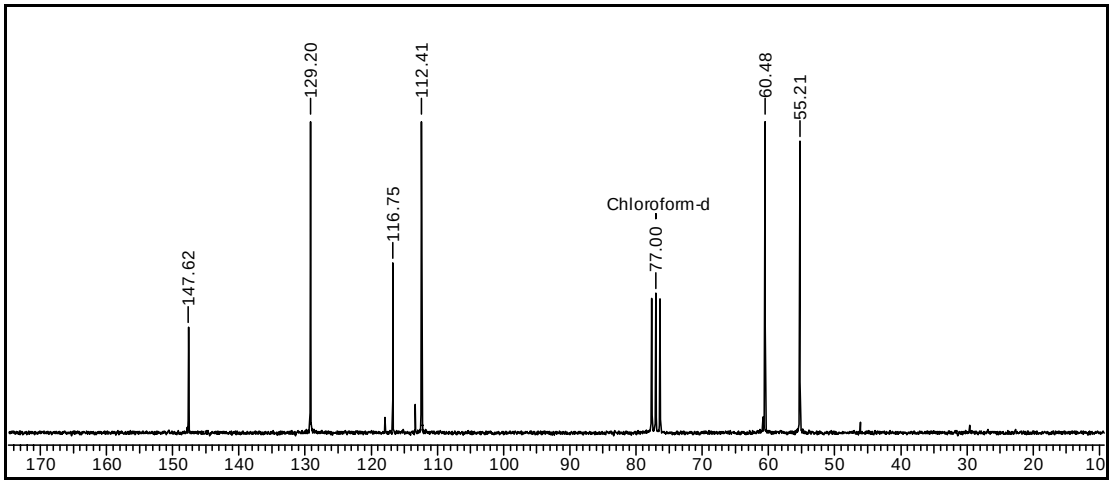
IR Spectrum of compound **3d** (film)



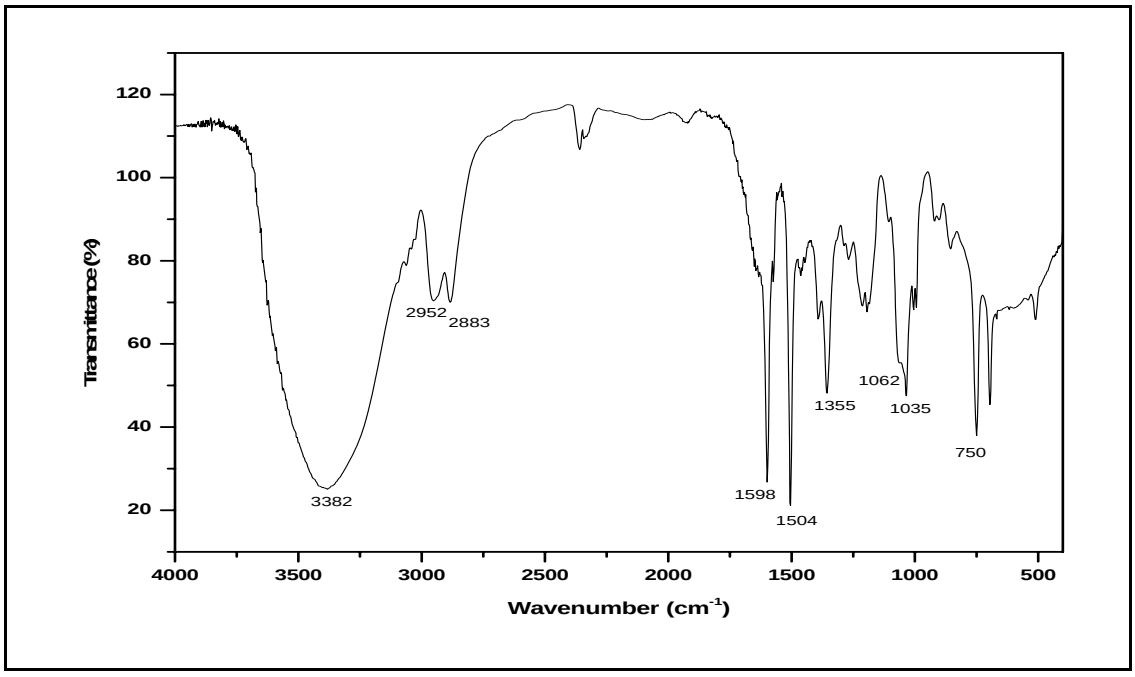
GC-MS Spectrum of compound **3d** (70 eV, EI)



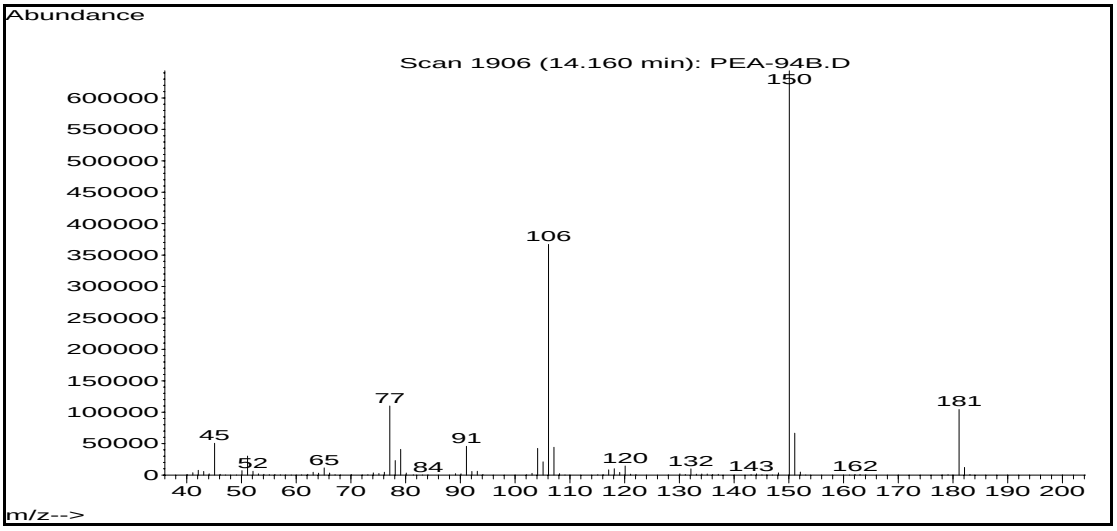
^{1}H NMR Spectrum of compound **4** ($CDCl_3$, 200 MHz) (NPDEA)



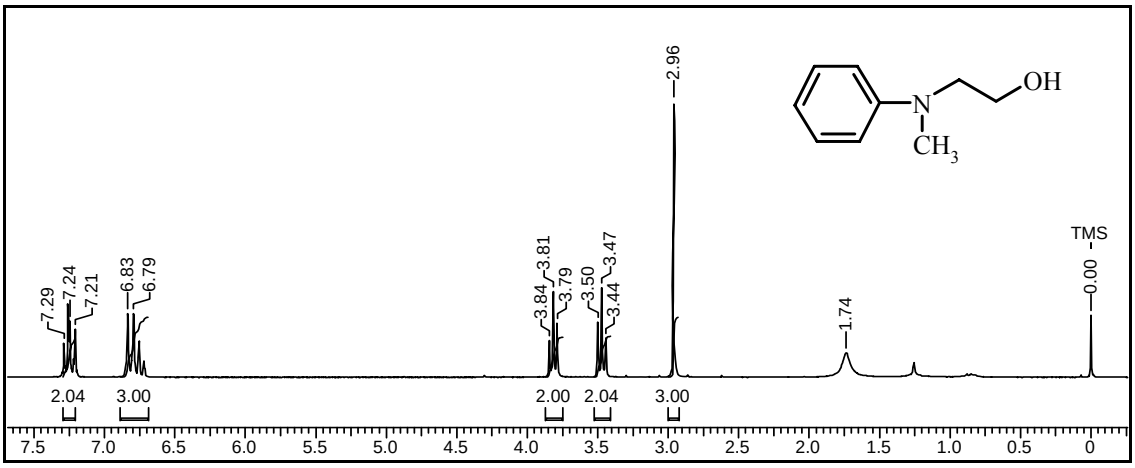
^{13}C NMR Spectrum of compound **4** ($CDCl_3$, 50 MHz)



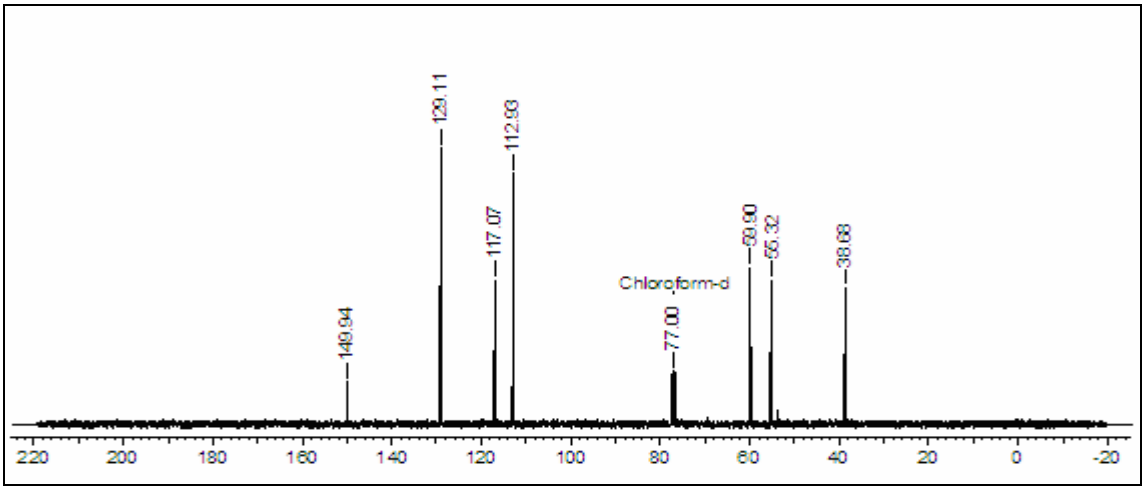
IR Spectrum of compound **4** (film)



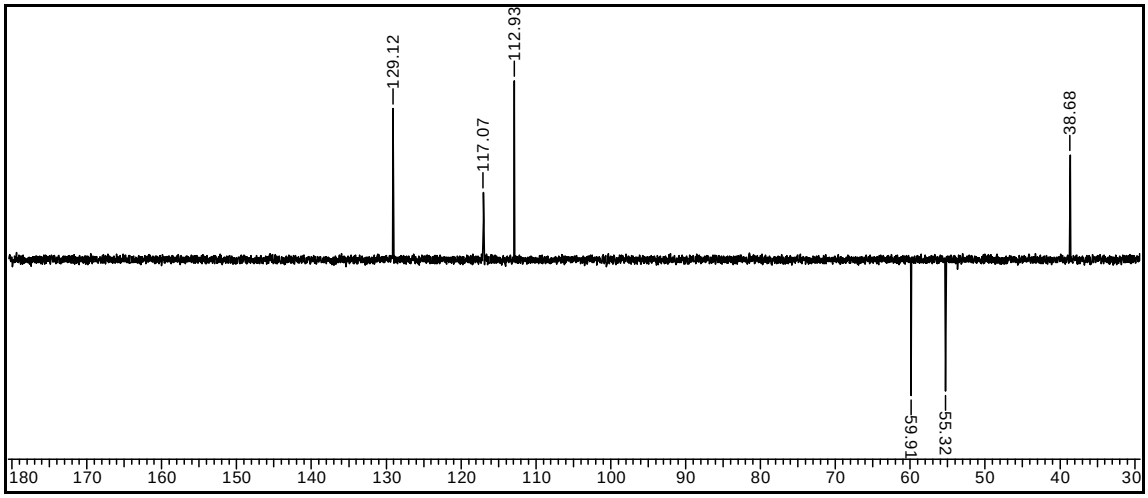
GC-MS Spectrum of compound **4** (70 eV, EI)



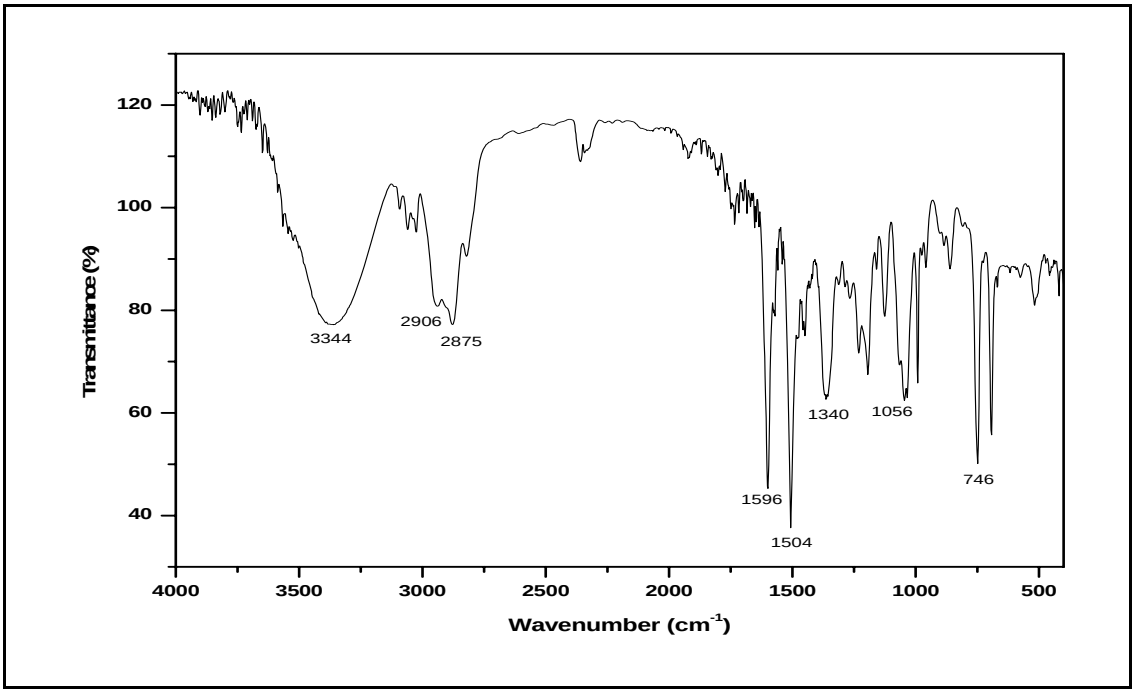
^{1}H NMR Spectrum of compound 7 ($CDCl_3$, 200 MHz)



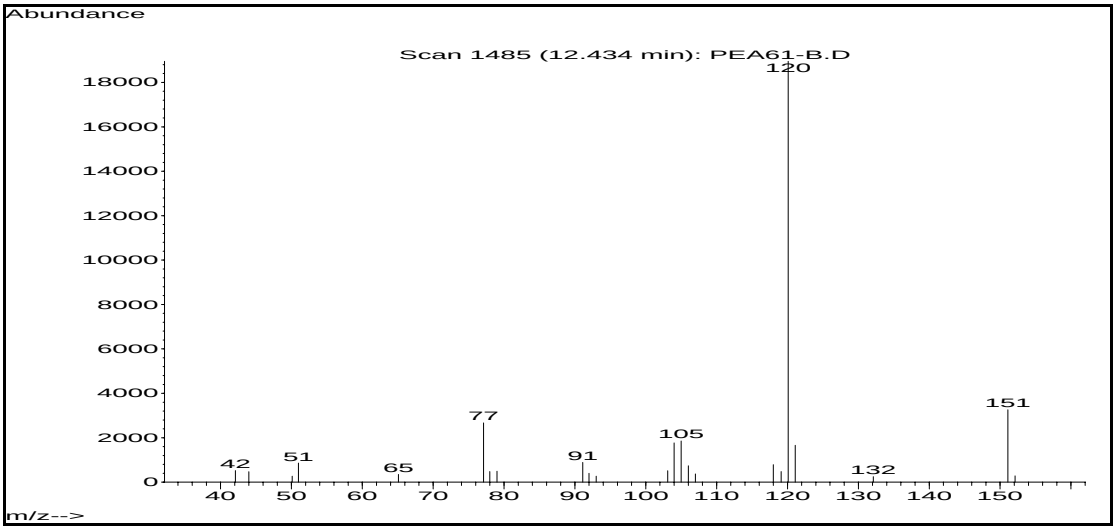
^{13}C NMR Spectrum of compound 7 ($CDCl_3$, 100 MHz)



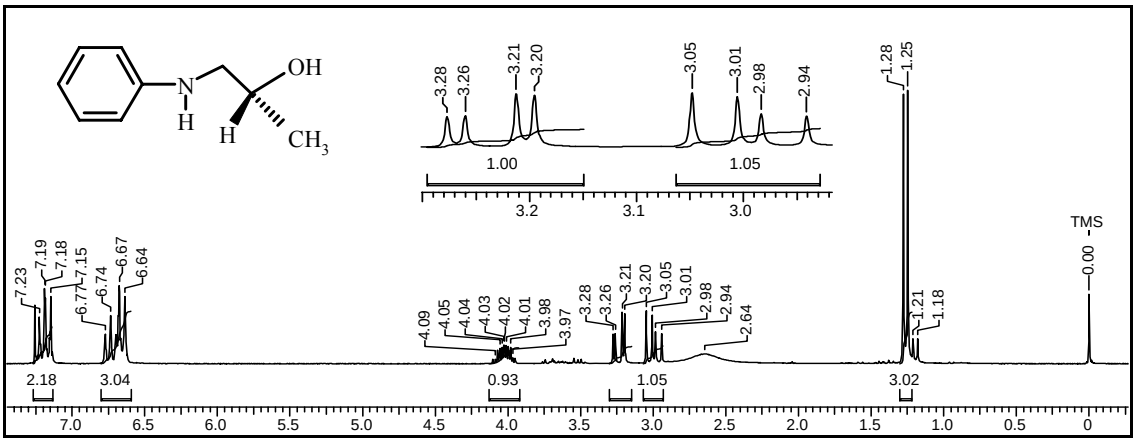
DEPT Spectrum of compound 7 ($CDCl_3$, 100 MHz)



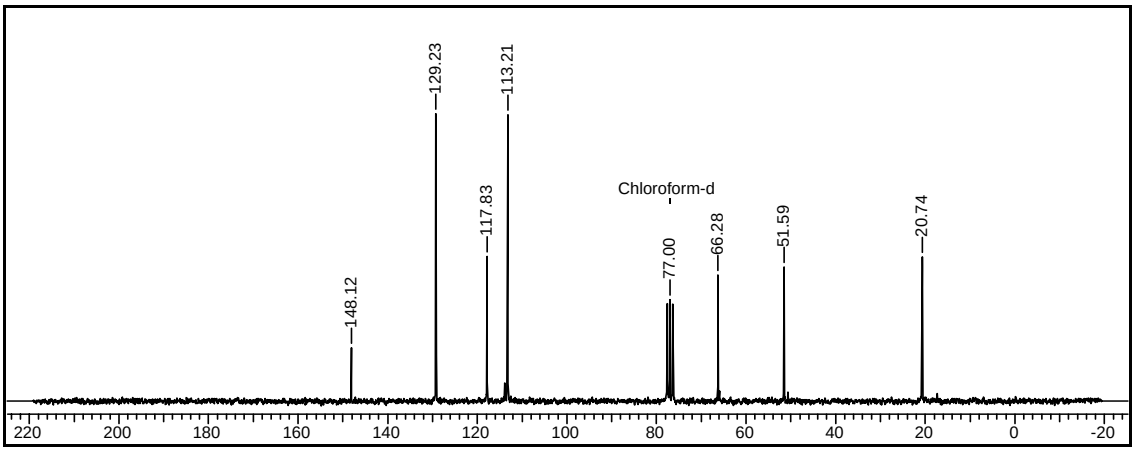
IR Spectrum of compound 7 (film)



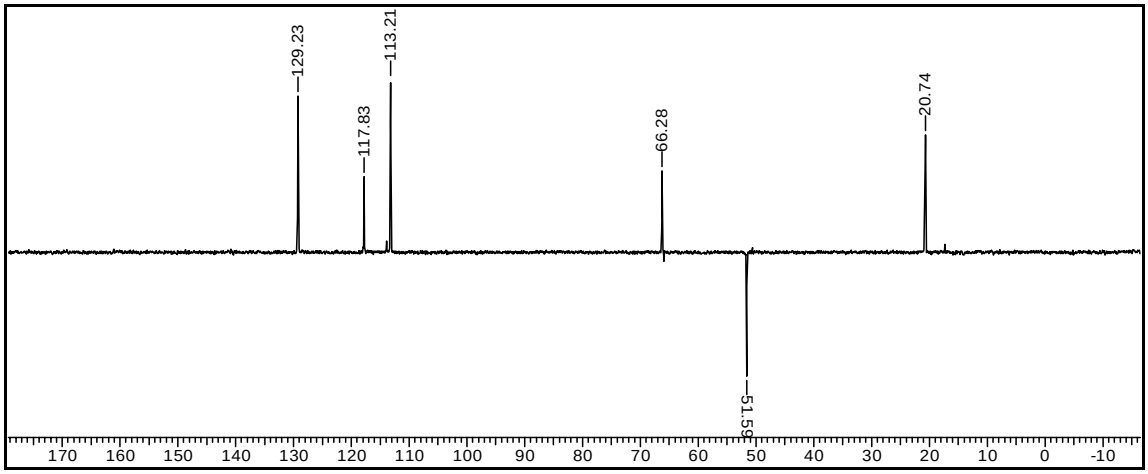
GC-MS Spectrum of compound 7 (70 eV, EI)



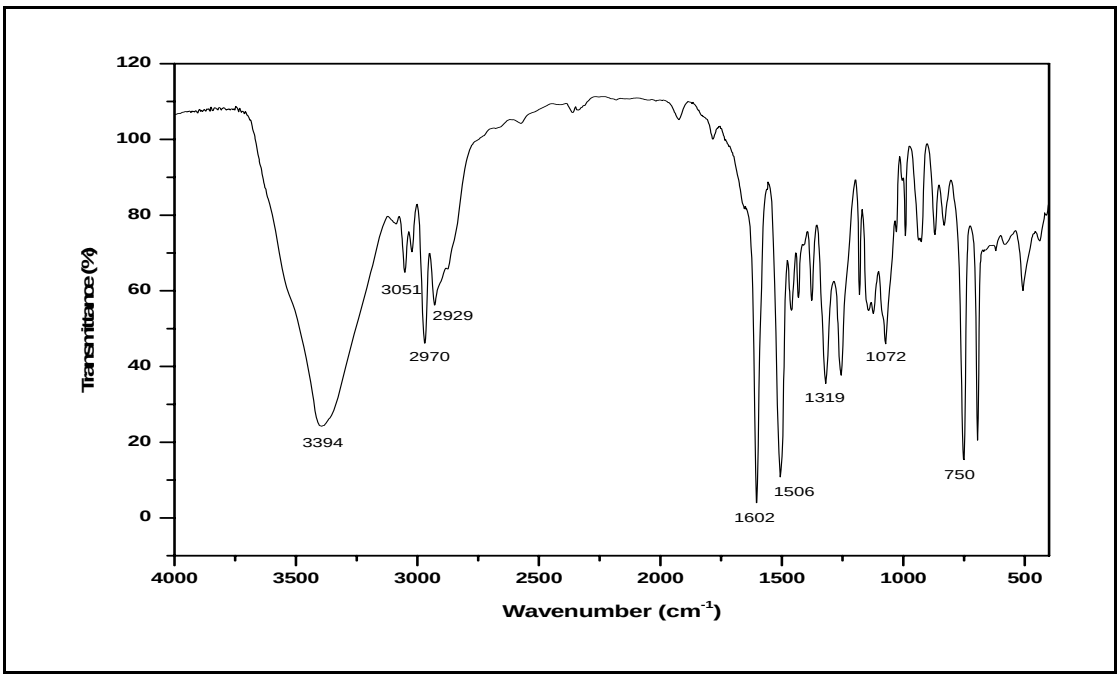
^{1}H NMR Spectrum of compound **13a** (96% purity; $CDCl_3$, 200 MHz)



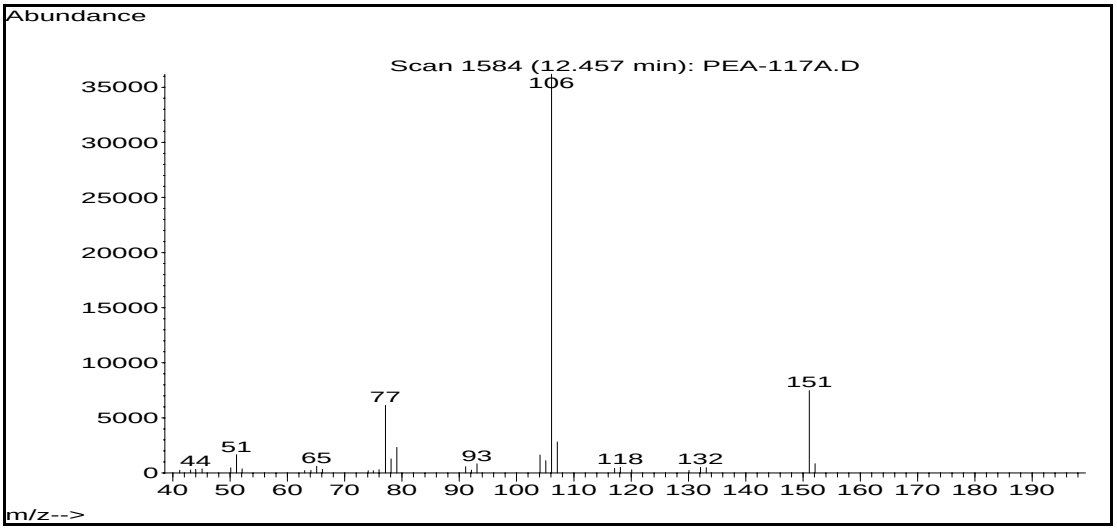
^{13}C NMR Spectrum of compound **13a** ($CDCl_3$, 50 MHz)



DEPT Spectrum of compound **13a** ($CDCl_3$, 50 MHz)



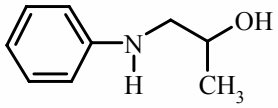
IR Spectrum of compound **13a** (film)



GC-MS Spectrum of compound **13a** (70 eV, EI)

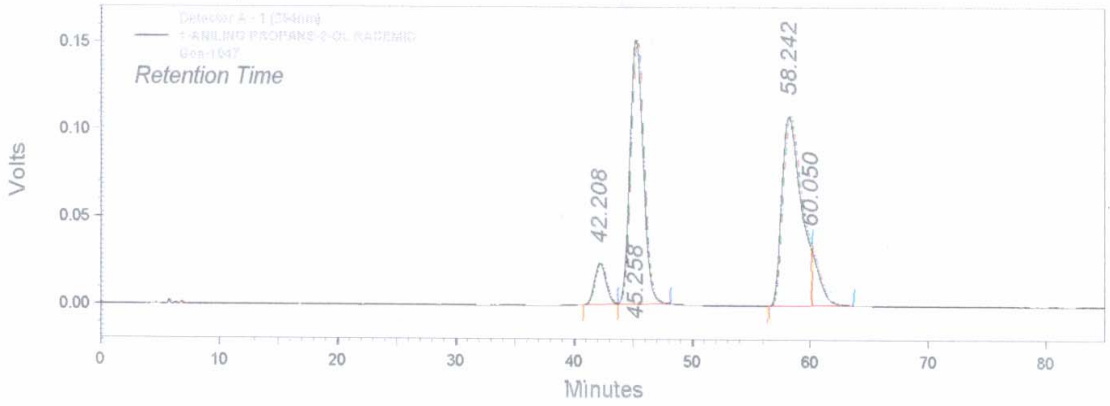
Shimadzu

Sample ID : 1-ANILINO PROPANE-2-OL RACEMIC
Method name : C:\CLASS-VP\Methods\Purity_vp.met
File name : C:\CLASS-VP\Data\GENERAL\Gen-1047
Accquisition time : 1/5/06 12:44:40 PM



(±) 1-anilinopropane-2-ol

Data Graph



Run Report

Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area Percent
1	42.208	1586973	5.86
2	45.258	11788271	43.54
3	58.242	12004059	44.34
4	60.050	1695226	6.26
Totals		27074529	100.00

COLUMN :Chiral OD-H 25cm
MOBILE PHASE :IPA:PET ETHER 2.5:97.5
WAVELENGTH :254 nm
FLOW ARTE :1.0 ml/min

Chiral HPLC Spectrum of compound (**10a + 11a)**

Shimadzu

Sample ID : 1-ANILINO PROPANE-2-OL R (PEA-117)
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File name : C:\CLASS-VP\Data\GENERAL\Gen-1048
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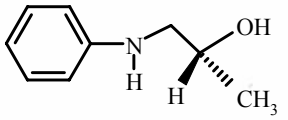
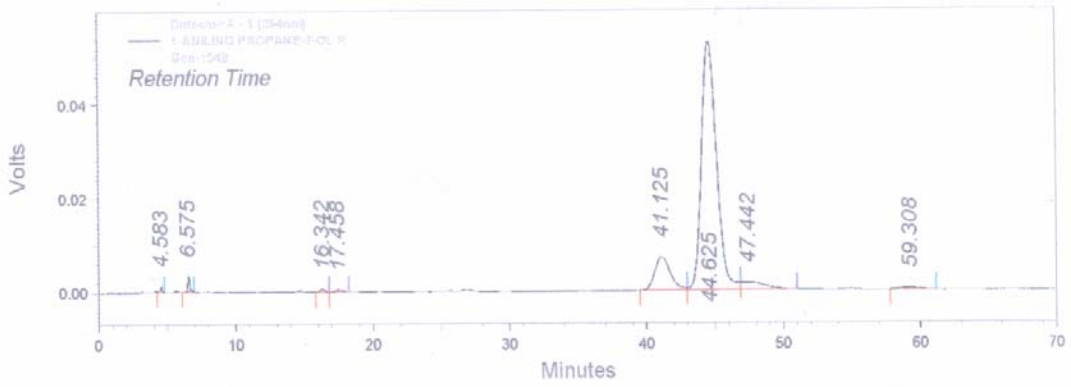


13a
(2R)- 1-anilinopropane-2-ol

Data Graph



Run Report

Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area Percent
1	4.583	11363	0.23
2	6.575	34087	0.70
3	16.342	15049	0.31
4	17.458	15091	0.31
5	41.125	560699	11.49
6	44.625	4026207	82.47
7	47.442	185101	3.79
8	59.308	34241	0.70
Totals		4881838	100.00

COLUMN :Chiral OD-H 25cm
MOBILE PHASE :IPA:PET ETHER 2.5:97.5
WAVELENGTH :254 nm
FLOW ARTE :1.0 ml/min

Chiral HPLC Spectrum of compound **13a**

Shimadzu

Sample ID : 1-ANILINO PROPANE-2-OL'S'(PEA 122)
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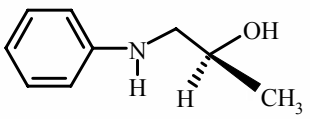
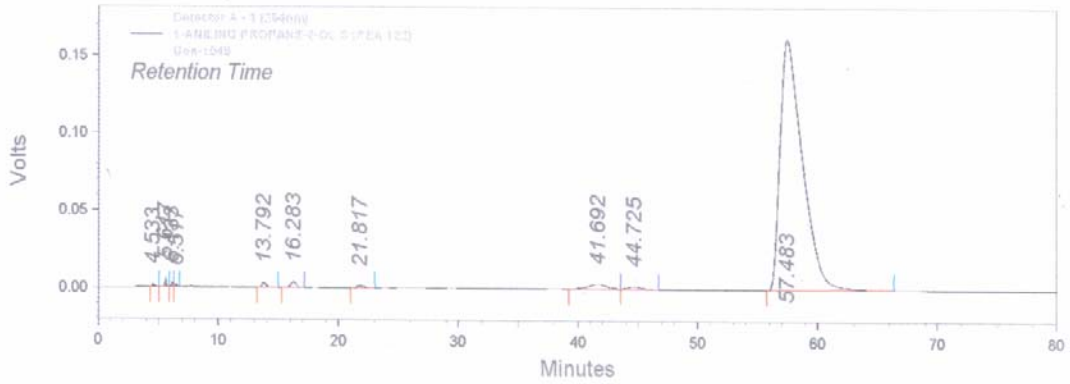
File name : C:\CLASS-VP\Data\GENERAL\Gen-1049
Accquisition time : 1/5/06 3:47:39 PM



13b
(2S)- 1-anilinopropane-2-ol

Data Graph



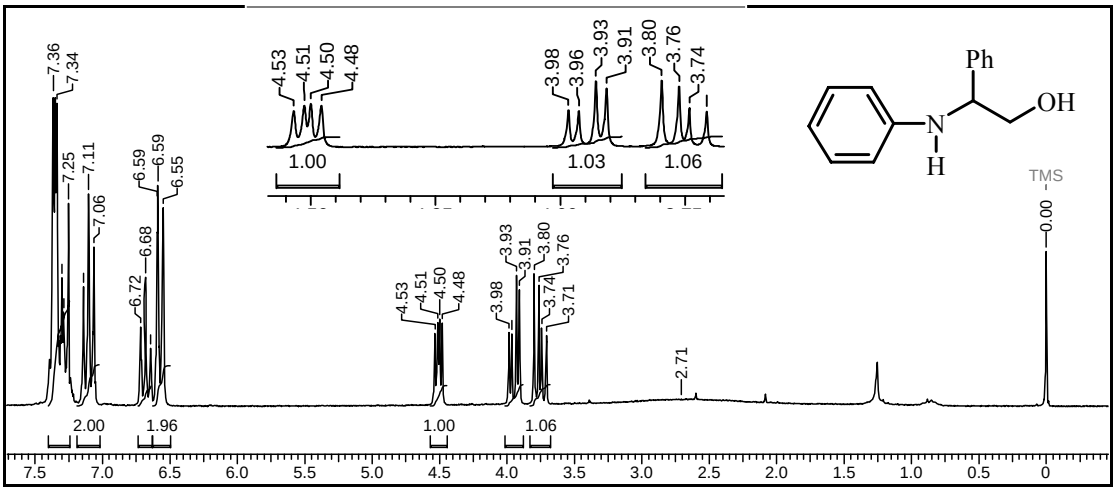
Run Report

Detector A - 1 (254nm)

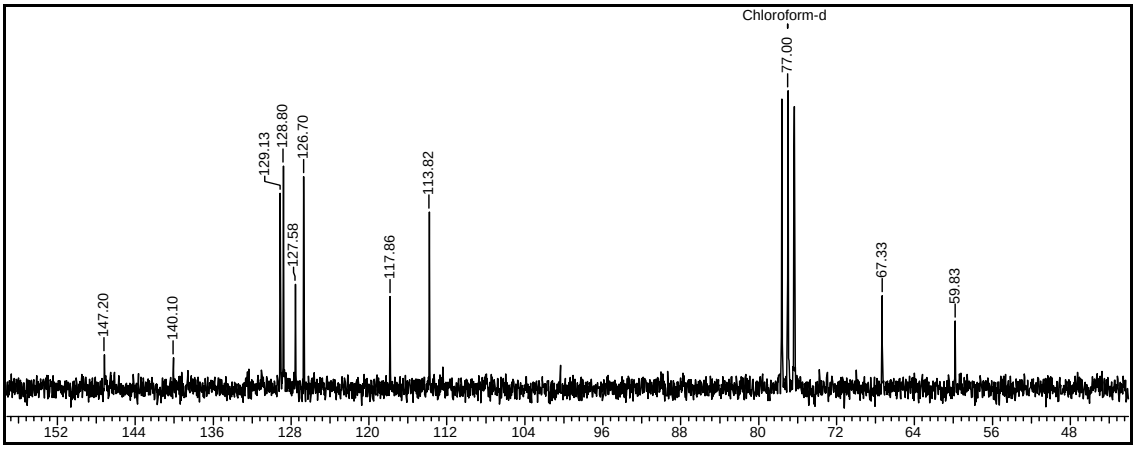
Pk #	Retention Time	Area	Area Percent
1	4.533	21147	0.10
2	5.617	43510	0.20
3	6.133	26522	0.12
4	6.517	14911	0.07
5	13.792	72219	0.33
6	16.283	119742	0.55
7	21.817	66549	0.31
8	41.692	356484	1.64
9	44.725	144084	0.66
10	57.483	20869714	96.02
Totals		21734882	100.00

COLUMN :Chiral OD-H 25cm
MOBILE PHASE :IPA:PET ETHER 2.5:97.5
WAVELENGTH :254 nm
FLOW ARTE :1.0 ml/min

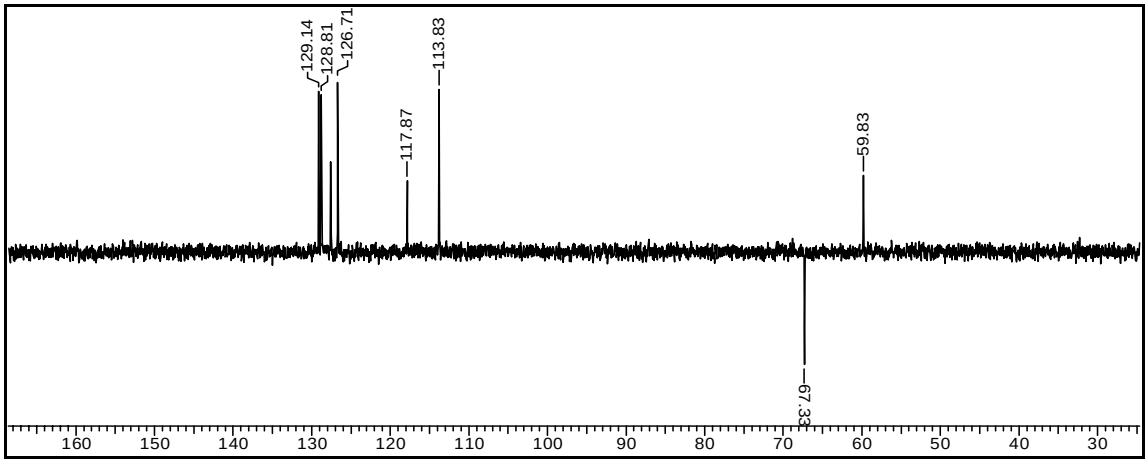
Chiral HPLC Spectrum of compound **13b**



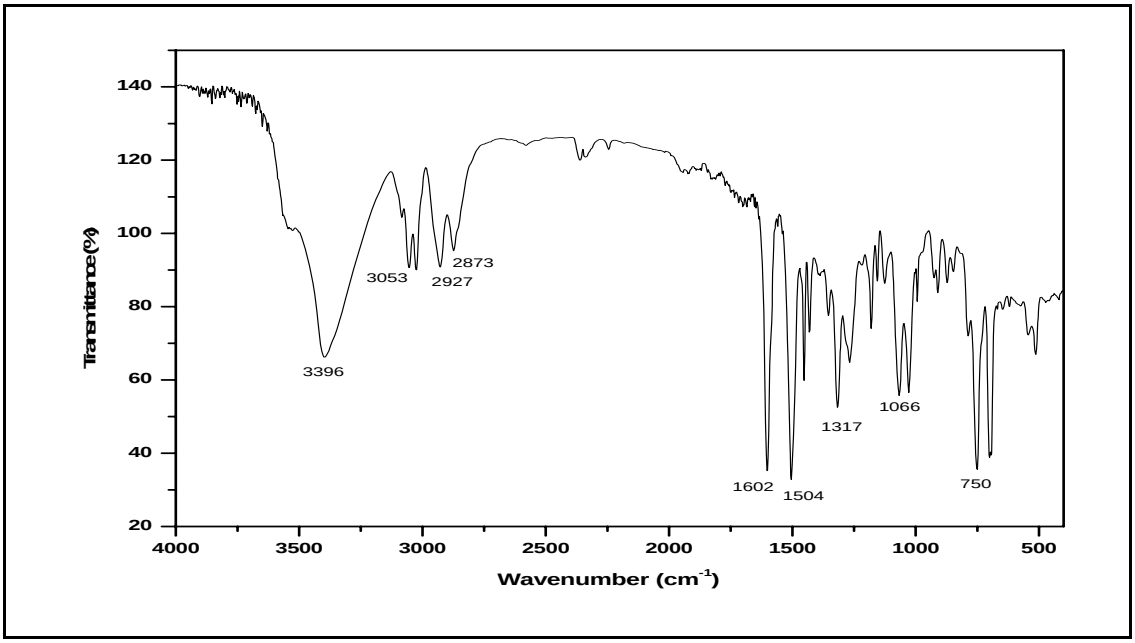
^{1}H NMR Spectrum of compound **11b** ($CDCl_3$, 200 MHz)



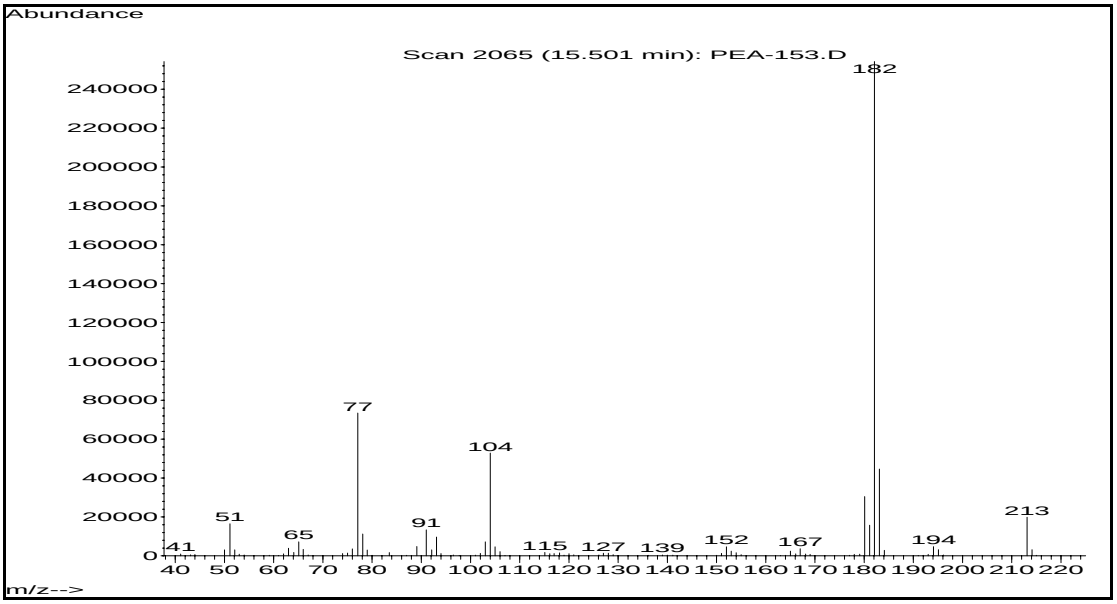
^{13}C NMR Spectrum of compound **11b** ($CDCl_3$, 50 MHz)



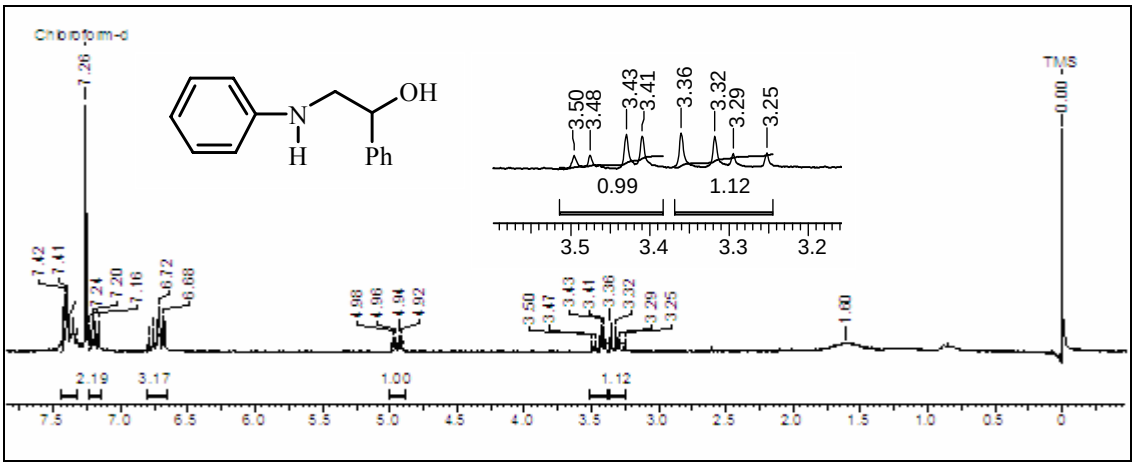
DEPT Spectrum of compound **11b** ($CDCl_3$, 50 MHz)



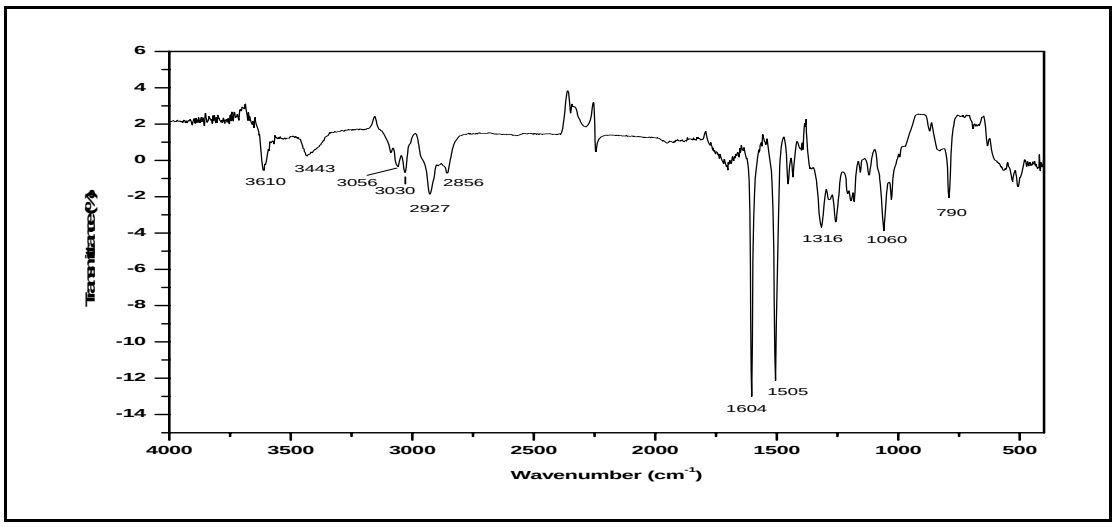
IR Spectrum of compound **11b** (film)



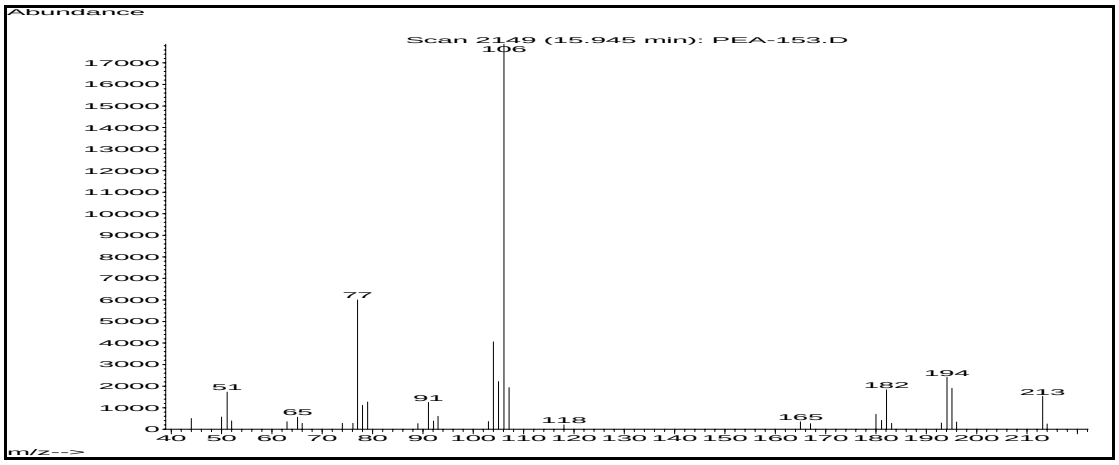
GC-MS Spectrum of compound **11b** (70 eV, EI)



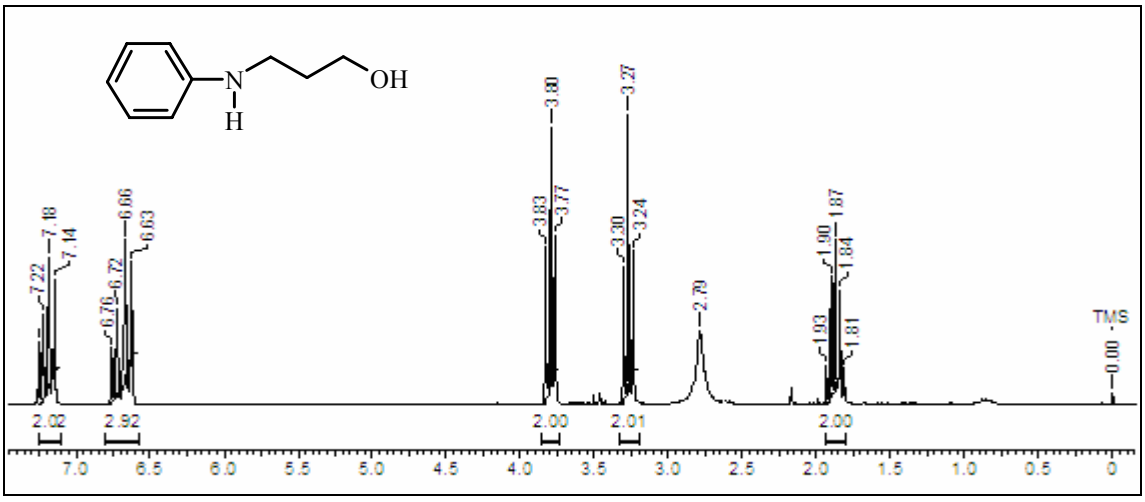
^{1}H NMR Spectrum of compound **10b** ($CDCl_3$, 200 MHz)



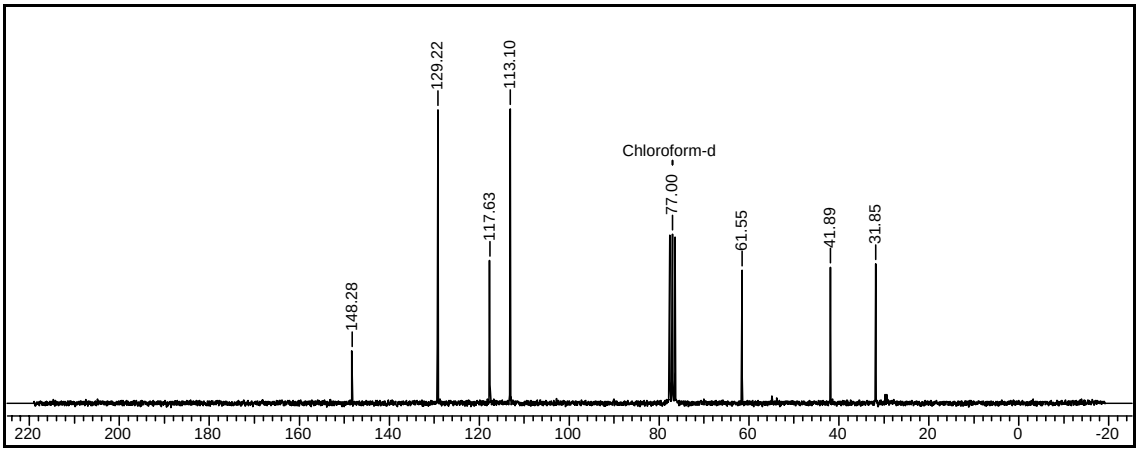
IR Spectrum of compound **10b** (in $CHCl_3$)



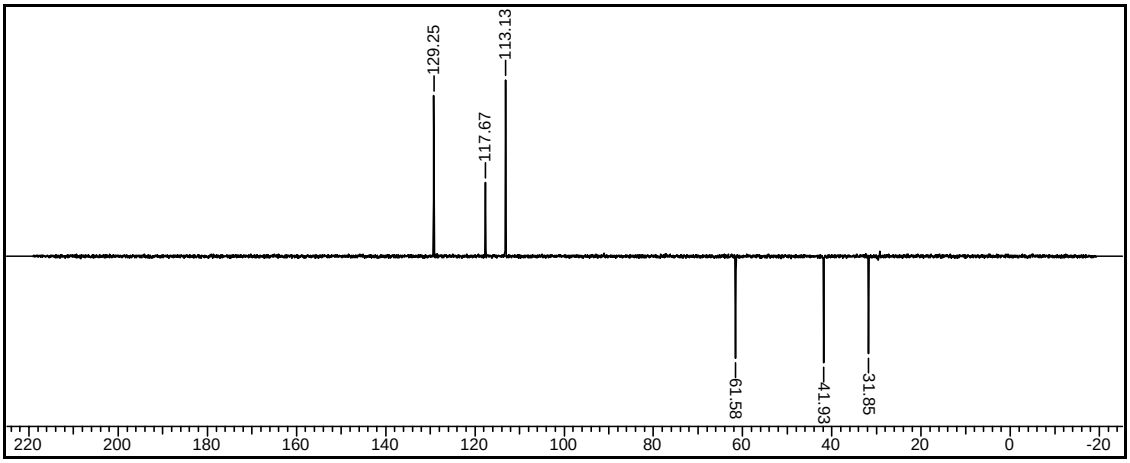
GC-MS Spectrum of compound x (70 eV, EI)



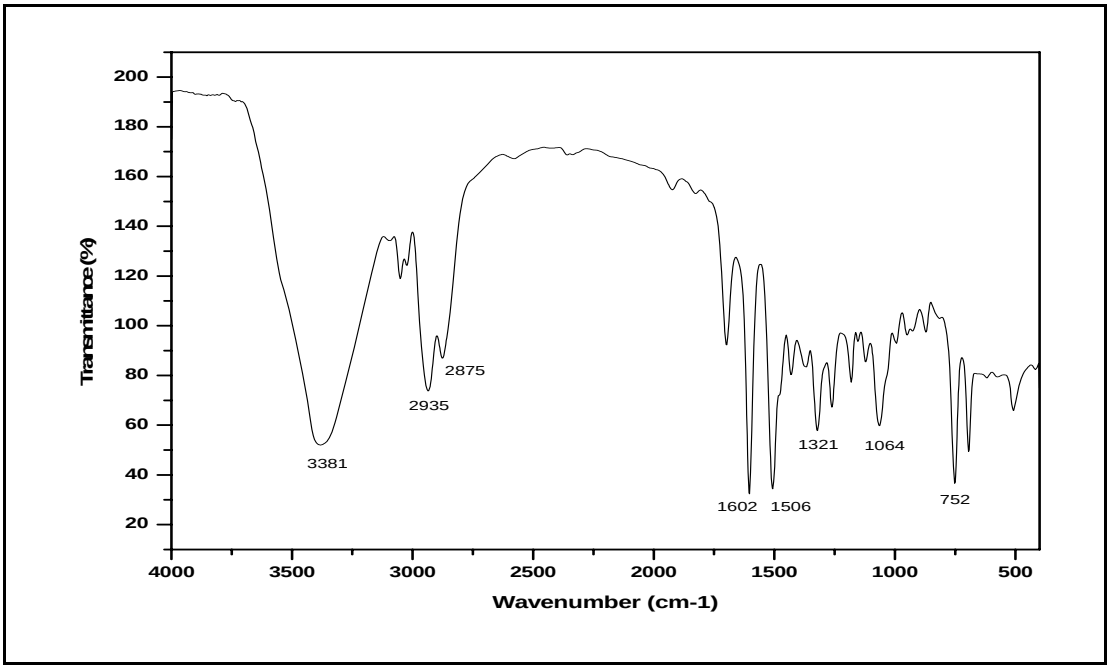
^{1}H NMR Spectrum of compound **12** ($CDCl_3$, 200 MHz)



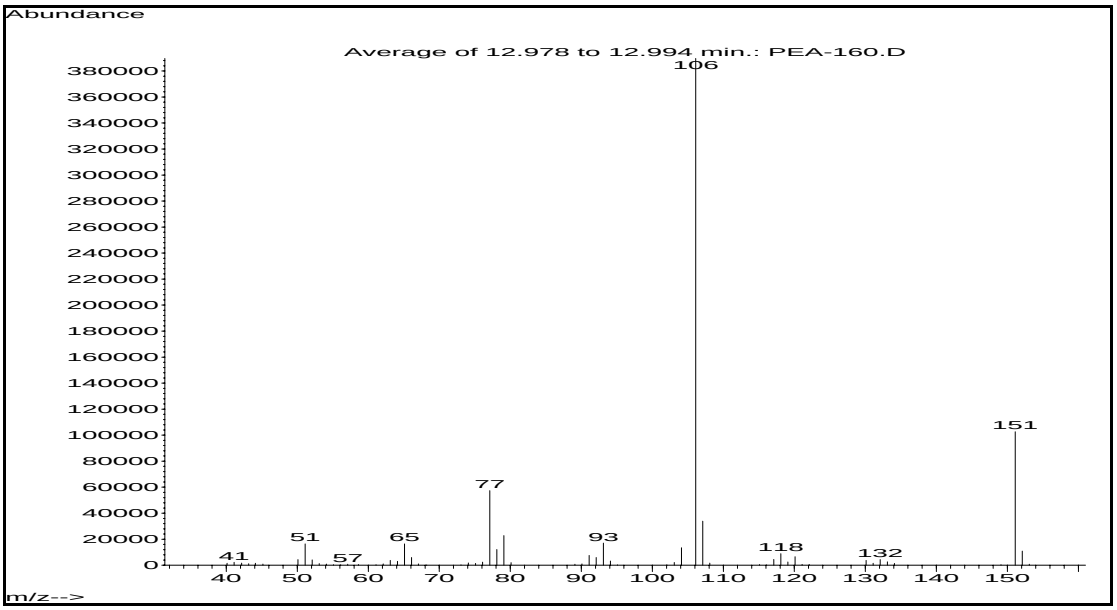
^{13}C NMR Spectrum of compound **12** ($CDCl_3$, 50 MHz)



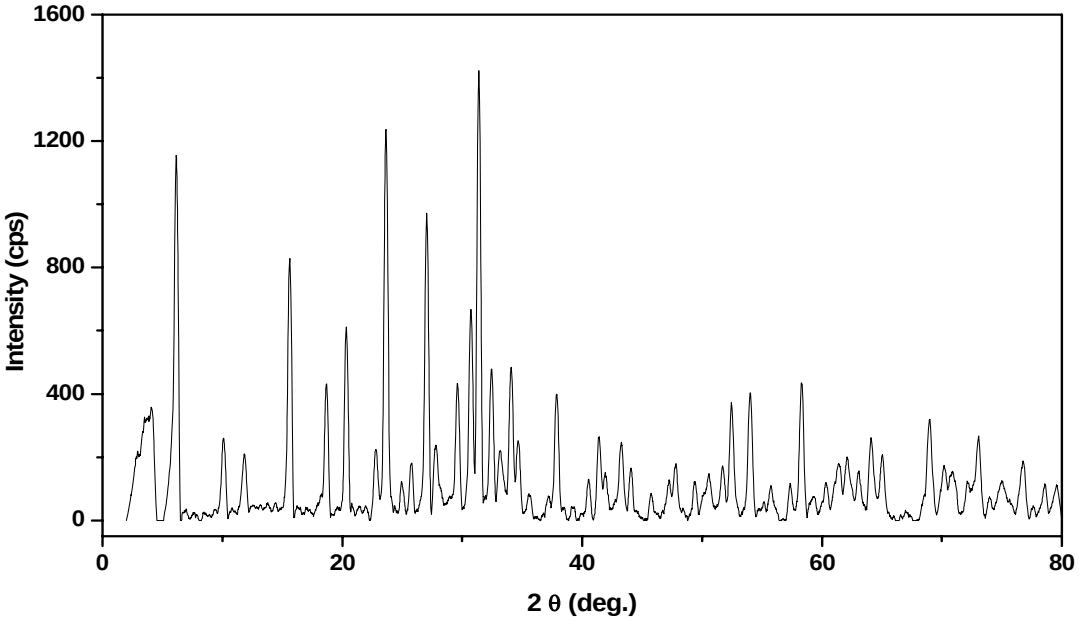
DEPT Spectrum of compound **12** ($CDCl_3$, 50 MHz)



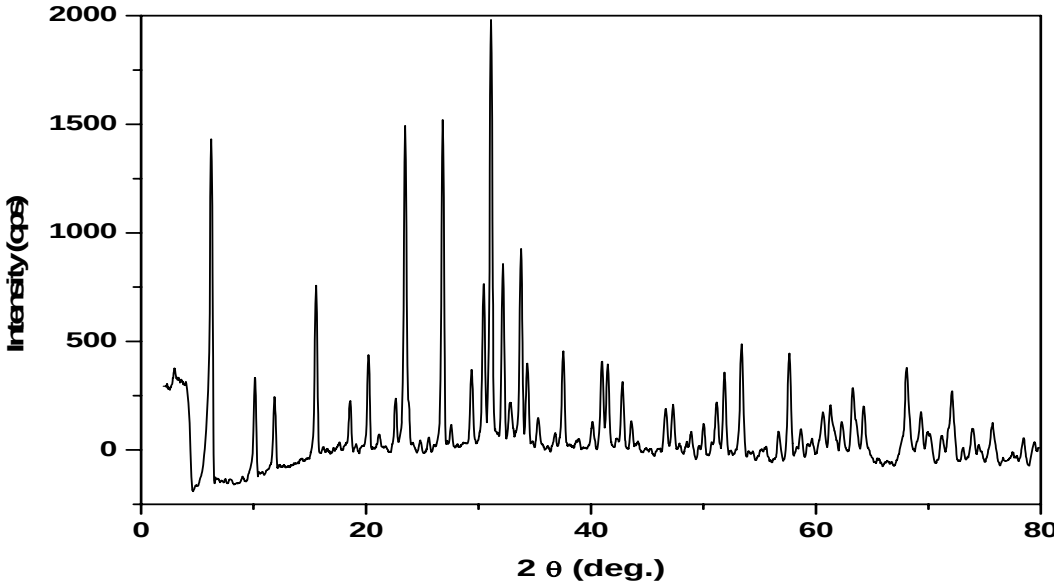
IR Spectrum of compound **12** (film)



GC-MS Spectrum of compound **12** (70 eV, EI)



XRD Spectrum of Na-Y zeolite



XRD Spectrum of Na-X zeolite

Chapter 5

Kinetic and Mechanistic Study of β-amino alcohol Synthesis from Aniline and Ethylene Carbonate Using Na-Y Zeolite as Catalyst

PART I

5.1. KINETIC STUDY OF *N*-ALKYLATION OF ANILINE BY ETHYLENE CARBONATE USING Na-Y ZEOLITE

5.1.1. INTRODUCTION

N-alkylation of anilines by alkylene carbonates is an important reaction for the synthesis of β-amino alcohols. A majority of studies appeared in the literature for β-amino alcohols synthesis on aminolysis of epoxides mainly focused on improving the catalytic performance and product selectivity whereas *N*-alkylation of aromatic amines using alkylene carbonate was not well investigated (Chapter 1, Table 1.10). A detailed investigation on catalytic activity of Na-Y zeolite as catalyst and it's reusability, effect of substrates and product selectivity was discussed in Chapter 4. However, knowledge of the reaction kinetics is also essential, as it describes the variation of reaction rate with temperature and concentration of different species involved in the reaction. Analyzing the influence of different reaction conditions on the reaction rate gives information about the reaction mechanism and the transition state of a chemical reaction. Also, the kinetic data are most essential in developing a rate equation that can be used for design and scale-up purposes. Selva et al.[1] have studied the kinetics of *N*-methylation of aromatic priamary amines by alkyl methyl carbonate using Na-Y zeolite as catalyst. Their results showed that a first order dependancy of aniline reaction rate at lower concentration of carbonate and zero order dependancy of aniline reaction rate at higher concentration of carbonate. Literature survey revels that there are no reports on kinetic study of *N*-alkylation of aromatic amines using alkylene carbonates.

The aim of this work was to study the kinetics of *N*-alkylation of aniline by ethylene carbonate using Na-Y zeolite. Various reaction parameters such as catalyst loading effect, solvent effect and concentration of aniline and ethylene carbonate on the rate of *N*-alkylation reaction were studied for a temperature range of 393 to 433 K. Different empirical rate models were considered, out of which a suitable rate equation was considered, which explained the experimental trends and the kinetic parameters were also evaluated.

5.1.2. EXPERIMENTAL SECTION

5.1.2.1. Materials

Aniline was purchased from M/S S.D. fine-chem. ltd. India. Ethylene carbonate and tri ethylene glycol dimethyl ether (triglyme) were purchased from Aldrich chemicals, USA. Faujasites Na-Y was provided by Süd-Chemie, India. Aniline was distilled prior to use. Fine powdered Na-Y zeolite was activated in air at 823 K for 6 h and then stored at 373 K in oven. The specification of Na-Y zeolite was as follows: Si/Al, 2.4; particle size, 6.5-7.5 $\times 10^{-7}$ m; surface area, 6×10^5 m^2/Kg; particle density, 2.5×10^3 Kg/m^3; porosity[2] (ε), 0.3; tortuosity[2] (τ), 3.

5.1.2.2. Reactor setup

A three-necked 30 ml flat bottom glass reactor of 3 cm internal diameter and 4.25 cm height equipped with 4 baffles and refluxing condenser was used for carrying out the reactions. The reactor was placed into an electrically heated oil bath equipped with digital temperature controller (HITECH, India). The desired speed of agitation was

achieved by controlling the speed of the magnetic stirrer having digital RPM display (REMI, India). A schematic diagram of the experimental set up is shown in Figure 5.1.

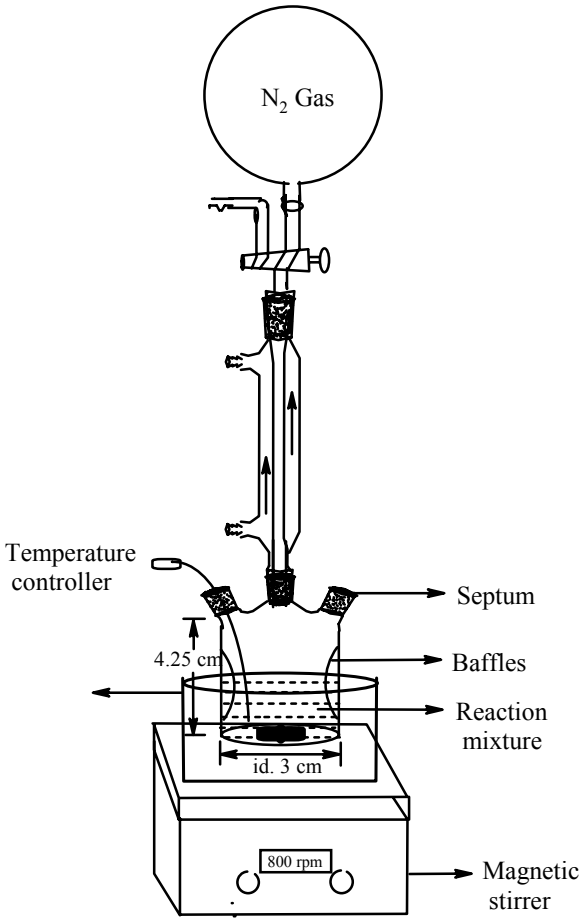


Figure 5.1: Experimental set up for *N*-alkylation reaction

5.1.2.3. Experimental procedure

In a typical experiment, known quantities of substrates, Na-Y catalyst and triglyme (solvent) were charged to reactor. The total volume of reaction charge was 10 ml. The reactor was purged with nitrogen and heated to desired temperature under nitrogen atmosphere. A typical speed of agitation of 13.3 Hz was employed. The reaction was continued for the specified time and intermediate liquid phase samples were

collected periodically. In each kinetic run all the liquid samples were analyzed by GC for concentration of reactants and products.

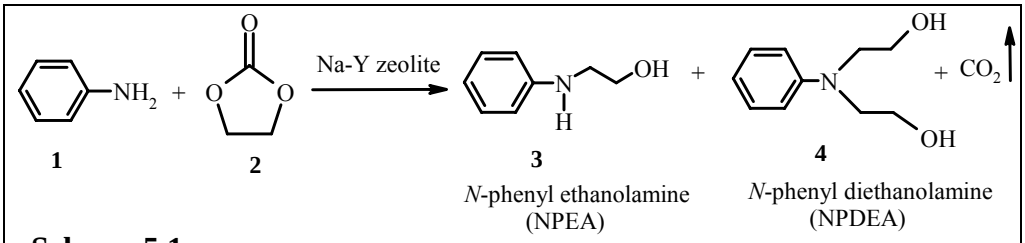
5.1.2.4. Analysis

Quantitative analysis of the liquid samples was carried on a Hewlett Packard 6890 Series GC equipped with auto sampler instrument by using HP-1 capillary column (30 m length × 0.32 mm i.d. × 0.25 μm film thickness, on 1% phenyl methyl siloxane stationary phase). The standard conditions for GC analysis were similar to that given in chapter 4 (Section 4.2.1.3).

5.1.3. RESULTS AND DISCUSSION

5.1.3.1. Preliminary experiments

Some preliminary experiments on *N*-alkylation of aniline by ethylene carbonate (EC) were carried out using the Na-Y zeolite as catalyst (Scheme 5.1) in order to select a range of reaction conditions suitable for studying the reaction kinetics and establish the product distribution, material balance etc. The range of reaction conditions under which the present study was carried out is given in Table 5.1.



Scheme 5.1

Table 5.1. Range of experimental conditions

Concentration of aniline (Kmol/m^3)	0.268 – 2.15
Concentration of ethylene carbonate (Kmol/m^3)	0.268 – 2.15
Temperature (K)	393 – 433
Concentration of Na-Y zeolite (Kg/ m^3)	1.25 – 15
Agitation speed (Hz)	6.6 – 16.6
Reaction volume (m^3)	1×10^{-5}

A typical concentration time-profile of *N*-alkylation of aniline by ethylene carbonate at a temperature of 433 K is shown in Figure 5.2. It was observed that both aniline and ethylene carbonate concentrations were decreased as a function of time, whereas concentration of NPEA was increased. From the concentration-time profile, it was observed that the material balance of the aniline and EC consumed and product NPEA formed was in the range of 95-99%. In few experiments CO_2 was measured by volumetric method and material balance was found up to 80-90%. Therefore, for kinetic study, concentration of CO_2 was not measured as the function of time for initial reaction rate calculations. Only those experiments were considered for the initial rate calculation in which the material balance as per the stoichiometry was grater than 96%.

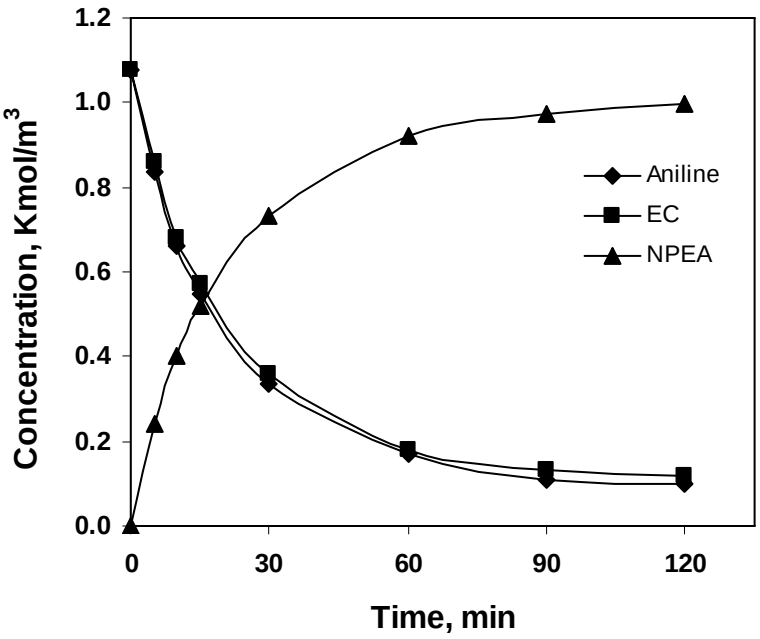
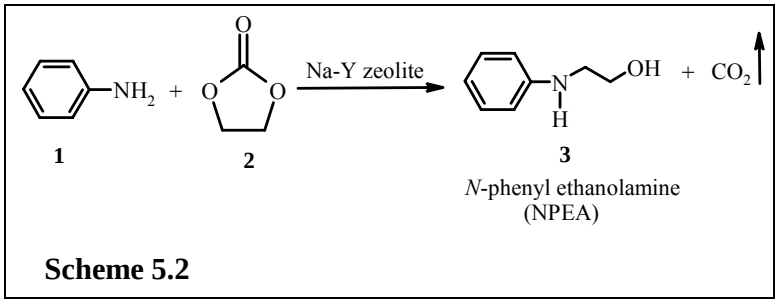


Figure 5.2. A typical concentration-time profile for *N*-alkyaltion of aniline by EC

Reaction conditions: aniline, 1.075 Kmol/m^3; ethylene carbonate, 1.075 Kmol/m^3; Na-Y catalyst, 10 Kg/m^3; Solvent, triglyme; T, 433 K; N_2 atmosphere; Time, 2h, Agitation speed, 13.3 Hz; Total volume, 10 ml.

Figure 5.2 shows that side-product *N*-phenyl diethanolamine (NPDEA) was not formed under experimental conditions. Hence, the reaction Scheme 5.1 can be simplified and shown as Scheme 5.2 from which NPDEA was excluded.



Scheme 5.2

5.1.3.1.1. Effect of solvent on NPEA yield

Few solvents with wide range of variation in their dielectric constants (Є) viz. triglyme ($Є^{20}$ = 7.6), 1-methyl-2-pyrrolidone (NMP, $Є^{20}$ = 32.4), ethylene glycol (EG, $Є^{20}$

= 37), *N,N*- dimethyl formamide (DMF, ϵ^{20} = 38.2) and ethylene carbonate (EC, ϵ^{40} = 90.5) were screened to investigate the effect of solvent on catalyst activity towards synthesis of β-amino alcohol (NPEA). These results are presented in Figure 5.3. The results showed that in highly polar medium (NMP, DMF, EG) yield of *N*-phenyl ethanolamine was poor (20–60%) as compared to less polar solvent, triglyme (100%). The effect of ethylene carbonate as solvent could not be compared, as EC is one of reactants. Though, EC worked as an excellent solvent, selectivity of NPEA (85% yield) was less due to the formation of by-product, *N*-phenyl diethanolamine (15% yield). Polar solvents such as DMF, NMP and EG interact strongly with the polar environment (i.e. a silicoaluminate structure) of the inner cages of Na-Y zeolite and becomes one of the major competitor of aniline for the active sites of the catalyst.[1a] Whereas, triglyme acts as a suitable anion activating media to perform the alkylation reaction and which allows operating the reaction at higher temperature in the range of 393 K – 453 K.[3] Therefore, for the kinetic study of *N*-alkylation reaction of aniline and ethylene carbonate, the experiments were carried out using triglyme as a solvent.

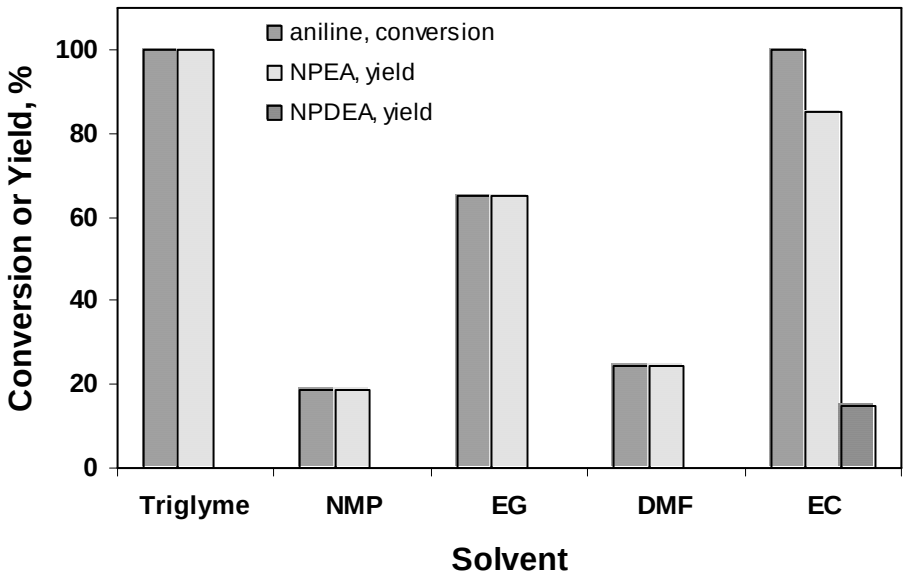


Figure 5.3. Effect of solvent on NPEA yield

Reaction conditions: aniline, 1.075 Kmol/m^3; ethylene carbonate, 1.075 Kmol/m^3; Na-Y catalyst, 15 Kg/m^3; T, 433 K; N_2 atmosphere; Time, 2 h, Agitation speed, 13.3 Hz; Total volume, 5 ml.

5.1.3.1.2. Effect of Na-Y zeolite pretreatment on its catalytic activity

The pretreatment of the catalyst can change its activity and selectivity in catalytic reactions, which is well known in catalytic hydrogenation reactions. Therefore, some experiments were carried out with the aim of understanding the effect of pretreatment of Na-Y catalyst with aniline and ethylene carbonate (Figure 5.4). For this purpose, Na-Y catalyst was treated first with any one of these substrates for 0.5 h at reaction temperature (433 K) followed by the addition of another substrate and then reaction was carried out for the specified time. The results indicated that the pretreated catalyst did not show any effect on catalytic activity. It was also confirmed here that initial rate of reaction was found to be unaffected by pretreatment. Therefore, for kinetic study, the experiments were carried out using Na-Y zeolite without any pretreatment.

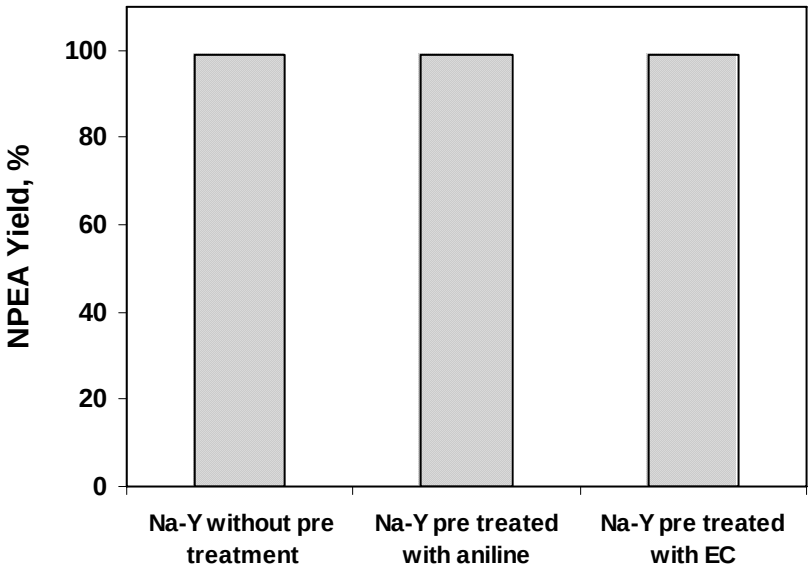


Figure 5.4. Effect of Na-Y catalyst pretreatment on NPEA yield

Reaction conditions: aniline, 1.075 Kmol/m^3; ethylene carbonate, 1.075 Kmol/m^3; Na-Y catalyst, 15 Kg/m^3; Solvent, triglyme; N_2 atmosphere; Time, 2 h, Agitation speed, 13.3 Hz; Total volume, 5 ml.

5.1.3.1.3. Effect of carbon dioxide atmosphere

In the synthesis of β-amino alcohol from aniline and ethylene carbonate, carbon dioxide was produced as a side product on the surface of Na-Y zeolite. It is assumed that CO_2 is evolved on the surface within the pores by chemical reaction and immediately transported from liquid filled pores to gas phase under reaction conditions (T, > 393 K). CO_2 diffuses out into the bulk liquid and eventually desorbed into gas phase (i.e. inert N_2) prevailing at liquid-gas phase boundary. In order to confirm that the reaction was not in mass transfer regime, two experiments were carried out to qualitatively show that CO_2 concentration on surface is inhibiting reaction. Firstly an experiment was carried out in CO_2 atmosphere (instead of inert gas N_2) and in the second experiment, nitrogen was bubbled through the liquid phase continuously so as to purge gas and liquid phases, the objective here was to drive away CO_2 from liquid as well as gas phase and thereby to see

whether reaction is facilitated. The concentration–time profile of *N*-phenyl ethanolamine is shown in Figure 5.5 (for the sake of convenience aniline and ethylene carbonate concentration profiles are not shown) along with standard reaction carried out under N_2 atmosphere. The data showed that under CO_2 atmosphere and in N_2 purge condition the concentration-time profile was the same as that was observed in N_2 atmosphere indicating that CO_2 had no effect on reaction rate. Therefore, further reactions were carried out in nitrogen atmosphere without purging gas phase.

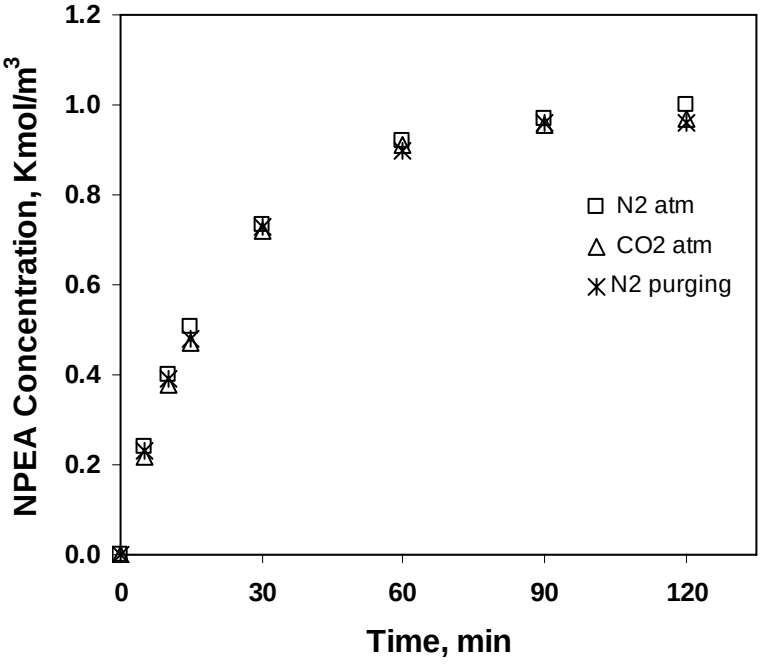


Figure 5.5. Comparison of Na-Y catalyst activity under N_2 and CO_2 atmosphere
Reaction conditions: aniline, 1.075 Kmol/m^3; ethylene carbonate, 1.075 Kmol/m^3; Na-Y catalyst, 10 Kg/m^3; Solvent, triglyme; T, 433 K; Time,2h, Agitation speed, 13.3 Hz; Total volume, 10 ml.

5.1.3.1.4. Effect of concentration of NPEA

The effect of concentration of product, *N*-phenyl ethanolamine (NPEA) was studied at 433 K in the range of 0.27 – 1.075 Kmol/m^3. In the experiments, predetermined amount of NPEA was added along with the substrates at the start of the

reaction and results are presented in Figure 5.6. The results showed that initial rate of reaction was not affected by concentration of NPEA indicating there was no reaction inhibition due to the liquid product (NPEA) concentration during the run.

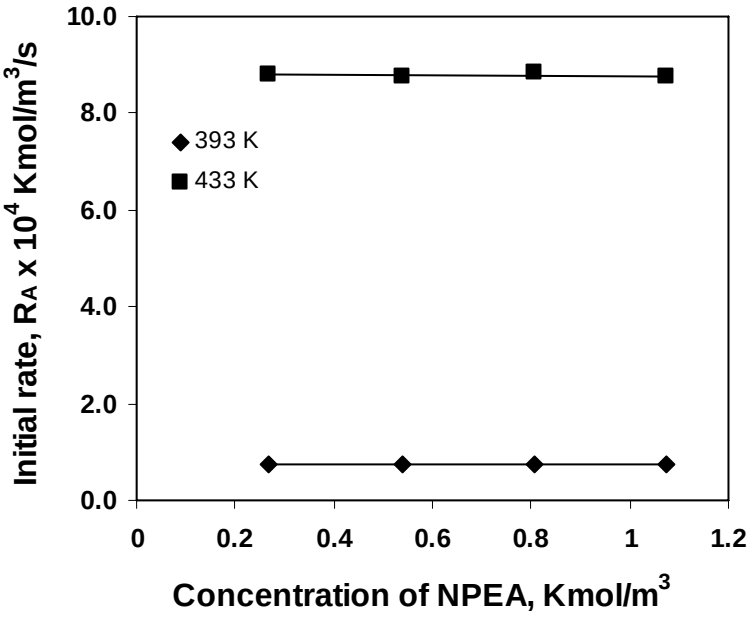


Figure 5.6. Effect of concentration of NPEA on initial rate of reaction

Reaction conditions: aniline, 1.075 Kmol/m^3; ethylene carbonate, 1.075 Kmol/m^3; NPEA; Na-Y catalyst, 10 Kg/m^3; Solvent, triglyme; N_2 atmosphere; Agitation speed, 13.3 Hz; Total volume, 10 ml.

5.1.3.1.5. Catalyst recycle study

It is important to ensure the consistent activity of the Na-Y catalyst through out a reaction. Otherwise, if catalyst deactivates during the reaction, reactor performance will be a function of catalyst deactivation rate and may give falsified kinetic parameters. The recycle of catalyst indicated that there was no appreciable drop in catalyst activity. The results showed that Na-Y zeolite was not deactivated due to the liquid-phase components as well as due to the gas-phase components.

5.1.4. ANALYSIS OF INITIAL RATE DATA

The analysis of initial rate data is useful in understanding the dependence of the reaction rate on individual reaction parameters and also in the evaluation of mass transfer effects. The initial rates of the reaction were calculated from the concentration time data, based on consumption of aniline concentration in the reaction. From these profiles the initial rate of aniline reaction, R_A, $(Kmol.m^{-3}.s^{-1})$ was calculated from the slope of concentration Vs time plots in the time interval of ~ 15 minutes. Similar plots were also made in few cases for ethylene carbonate and *N*-phenyl ethanol amine concentration and calculated rates of EC and NPEA based on initial time intervals were found to agree as per the stoichiometry depicted in scheme 5.2.

5.1.4.1. Effect of concentration of aniline

The effect of concentration of aniline on the rate of *N*-alkylation reaction was studied in the range of 0.268 – 2.15 Kmol/m^3 at 393, 413 and 433 K. The rate of reaction showed linear dependence on aniline concentration in the range studied. The graphical representation of the dependence of the reaction rate on aniline concentration is shown in Figure 5.7. The aniline concentration dependency on initial rate of reaction can be explained on the basis that either aniline is adsorbed on catalyst surface and has yet to saturate catalyst surface so that EC has enough vacant sites remaining for adsorption resulting in increase in reaction rates with increase in aniline concentration or is very weakly adsorbed such that ethylene carbonate is able to displace it and bring about the reaction. The third probability is that aniline is not adsorbed at all on catalyst and adsorbed ethylene carbonate reacts with aniline present in the pores of zeolite (Eley-

Rideal mechanism). These possibilities will be explored when kinetic rate model is evaluated in section 5.1.6.

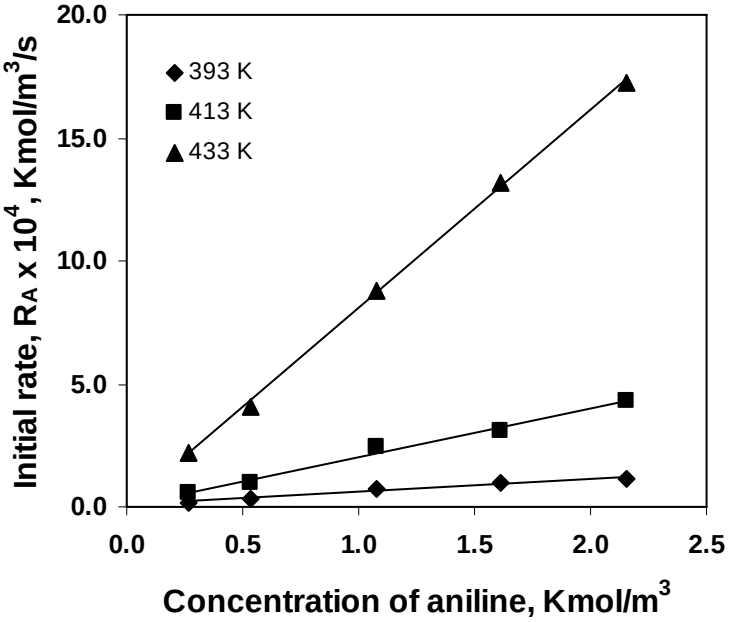


Figure 5.7. Effect of concentration of aniline on initial rate of reaction

Reaction conditions: aniline, 0.268 – 2.15 Kmol/m^3; ethylene carbonate, 1.075 Kmol/m^3; Na-Y catalyst, 10 Kg/m^3; Solvent, triglyme; N_2 atmosphere; Agitation speed, 13.3 Hz; Total volume, 10 ml.

5.1.4.2. Effect of concentration of ethylene carbonate

The effect of concentration of ethylene carbonate on the initial rate of *N*-alkylation reaction was studied in the range of 0.268–2.15 Kmol/m^3 at different temperatures (393 – 433 K) and the results are presented in the Figure 5.8. The rate was found to increase with increase in ethylene carbonate concentration up to 1.075 Kmol/m^3 and was found to decrease slowly with further increase of ethylene carbonate concentration. The rate behavior of ethylene carbonate concentration indicated that, with the increase in the concentration of ethylene carbonate, concentration of adsorbed ethylene carbonate increased resulting in increasing the rate of reaction. However, at

critical concentration of ethylene carbonate, catalyst surface got saturated with adsorbed ethylene carbonate and further increase in the amount of ethylene carbonate can not increase the rate. This effect was more prominent at higher temperature and less at lower temperature wherein reaction rates were low and catalyst surface was not saturated with ethylene carbonate. This trend supports the observation made in earlier section 5.1.4.1, that aniline adsorption may be very weak. If one assumes that amino alcohol was formed by reaction of adsorbed aniline and adsorbed ethylene carbonate, then in this case, at high EC concentration, competitive adsorption of EC and aniline would decrease availability of vacant site for aniline adsorption. And in this case reaction rate would decrease. However rate was not decreased with increase in EC concentration but remained constant indicating that assumption of aniline adsorption on catalyst surface was not correct. Selva et al. had reported similar dependency on reaction rate with alkyl methyl carbonate concentration for *N*-alkylation of aniline with Na-Y zeolite.[1]

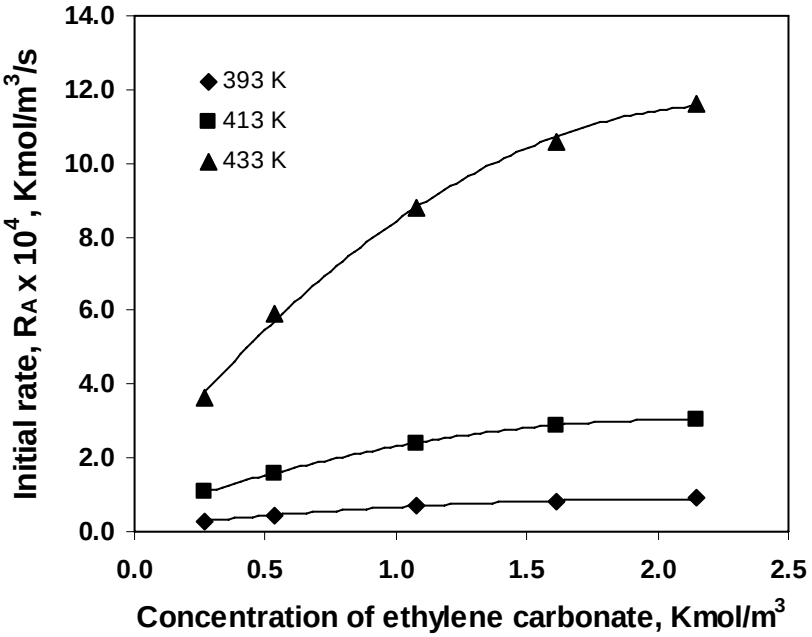


Figure 5.8. Effect of concentration of ethylene carbonate on initial rate reaction

Reaction conditions: aniline, 1.075 Kmol/m^3; ethylene carbonate, 0.268 – 2.15 Kmol/m^3; Na-Y catalyst, 10 Kg/m^3; Solvent, triglyme; N_2 atmosphere; Agitation speed, 13.3 Hz; Total volume, 10 ml.

5.1.5. ANALYSIS OF MASS TRANSFER EFFECTS

The chemical reaction in presence of a solid catalyst consists of physical as well as chemical steps, generally reactants has to be transported from bulk reactant phase to the active centers of the catalyst and product to be transported from catalyst surface to the bulk solvent or gas phases (Figure 5.9). In order to ascertain that the reaction is in kinetic regime, chemical reaction has to be slower compared to physical transport rates. A description of physical mass transfer steps is made in the following section when solid catalyst is used.

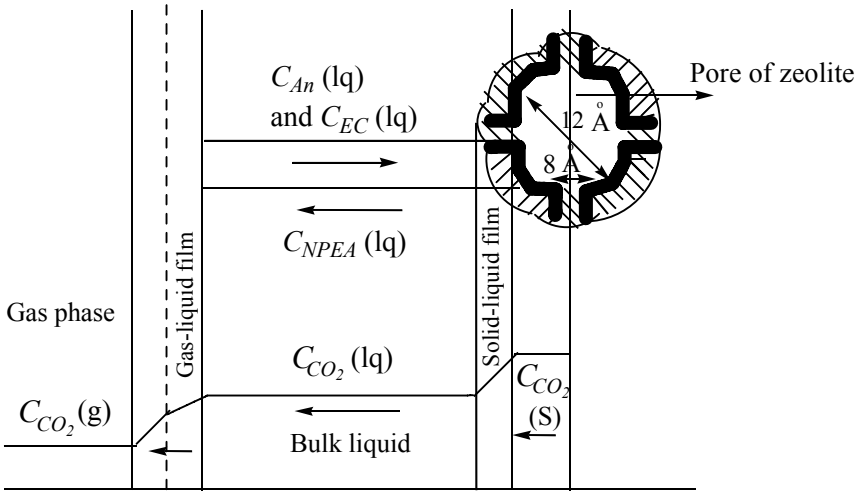


Figure5.9. Schematic presentation of mass transfer steps involved in *N*-alkylation of aniline by ethylene carbonate to *N*-phenyl ethanolamine

In a chemical process involving zeolite as catalyst usually the feed stream is in the gas or liquid phase, where *adsorption* on the zeolite surface and into the zeolite pores first has to take place. In order to react, the molecules then have to be transported to the reactive sites inside these pores. This transport process is called *diffusion*, which has two components; bulk diffusion that involves diffusion of molecules in bulk liquid or gas phase and pore diffusion that involves diffusion in catalyst pores. Diffusion in zeolites differs from ordinary diffusion in the sense that the molecules have to move through channels of molecular dimensions having electrostatic environment. As a result, there is a constant interaction between the diffusing molecules and the zeolite framework (see Figure 5.18 for Na-Y structure), and the molecular motion is thus also strongly influenced by the exact size and shape of these channels instead of the temperature and concentration only.

Once the reactants have reached the catalytically active sites, the necessary chemical reactions can finally take place, and the conversion into products takes place. At

this stage products have to be transported away from the micro channels of zeolite recreating free catalytic sites to facilitate the further reaction. As the conversion of reactants can only occur when a significant amount of them are able to reach the active sites, and the resulting products are removed sufficiently fast from these sites, one can imagine that both adsorption and diffusion can significantly determine the catalytic behavior of a system. These steps are schematically depicted in Figure 5.10.

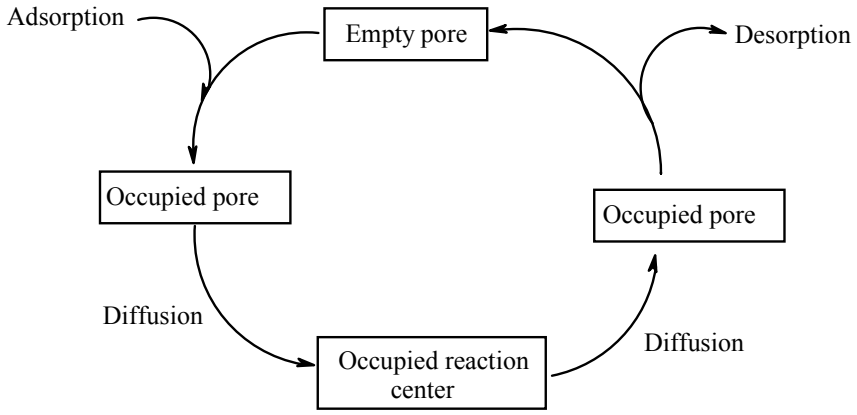


Figure 5.10. A catalytic cycle in zeolite catalysis[4]

In order to make sure that the chemical reaction is not limited by physical steps such as diffusion of reactant to the active site of catalyst and desorption of products from reaction centers to bulk phase, criteria available in literature to calculate the significance of mass transfer rates were employed.[5]

For the purpose of kinetic study it is important to ensure that, the rate data obtained are under kinetic regime and free from external liquid-solid mass transfer resistance and intra-particle diffusion resistance. Therefore following studies were carried out to analyze the significance of various mass transfer resistances in the range of experimental conditions.

5.1.5.1. Effect of agitation speed

The effect of agitation speed was checked at highest catalyst loading and highest temperature (used for kinetic study) to ascertain the liquid-solid mass transfer effect. Figure 5.11 shows the effect of agitation speed on the initial rate of aniline. It was found that stirrer speed has no effect on initial rate of aniline reaction indicating that reaction is free from external mass transfer barrier. Hence, all experiments for the present study were carried out at 13.3 Hz.

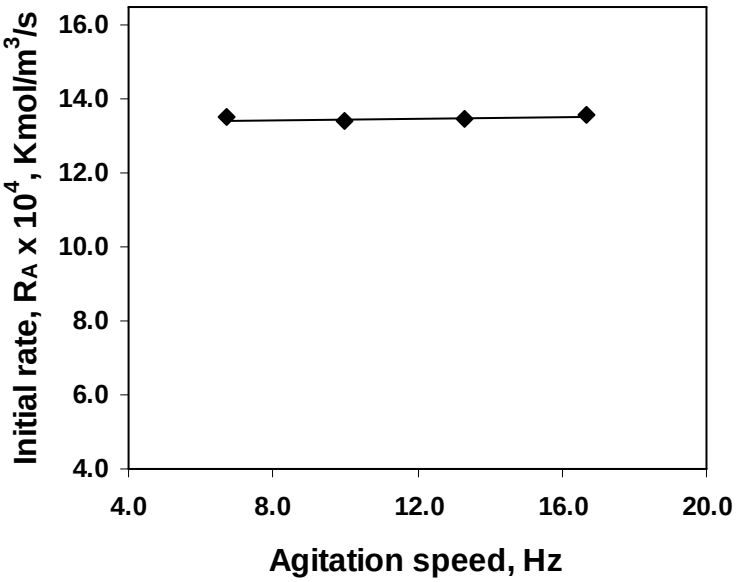


Figure 5.11. Effect of agitation speed on initial rate of reaction

Reaction conditions: aniline, 1.075 Kmol/m^3; ethylene carbonate, 1.075 Kmol/m^3; Na-Y catalyst, 15 Kg/m^3; Solvent, triglyme; T, 433 K; N_2 atmosphere; Total volume, 10 ml.

5.1.5.2. Effect of catalyst loading

Effect of catalyst loading on initial rate of *N*-alkylation reaction of aniline and ethylene carbonate was investigated in the range of 1.25 – 15 Kg/m^3 at 433 K and the results are presented in Figure 5.12. Initial rate of reaction showed linear dependence on

catalyst loading, indicating the absence of external liquid-solid mass transfer effects under the conditions of present work.[6]

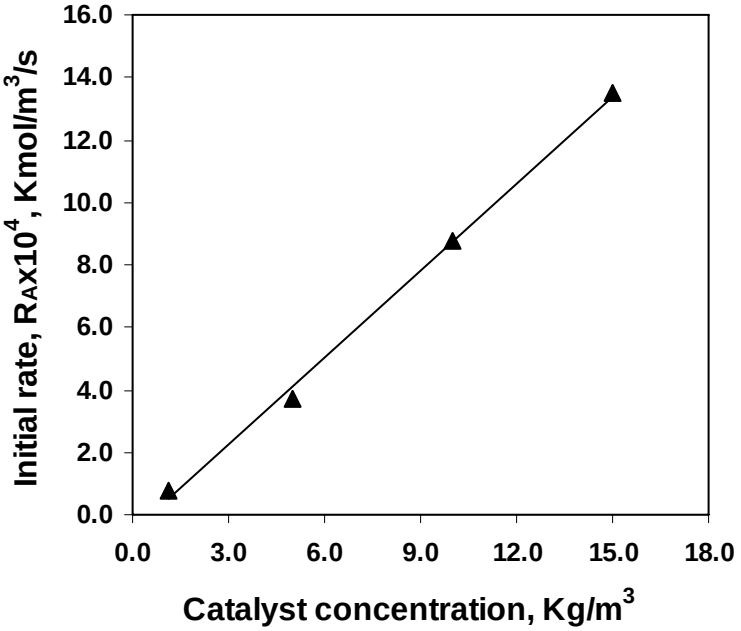


Figure 5.12. Effect of Na-Y zeolite catalyst loading on initial rate of reaction

Reaction conditions: aniline, 1.075 Kmol/m^3; ethylene carbonate, 1.075 Kmol/m^3; Na-Y catalyst; Solvent, triglyme; T, 433 K; N_2 atmosphere; Agitation speed, 13.3 Hz; Total volume, 10 ml.

5.1.5.3. Intra-particle diffusion resistance

Zeolites are crystalline three dimensional aluminosilicate materials having very regular structure, with open channels or cages and acidic and basic properties. For the zeolites, catalytically active sites are not directly accessible to the reacting molecules and therefore, a number of different mass transfer steps are required in order to convert the reactants into the desired products (Figure 5.9).

The fine powdered Na-Y zeolite, with average particle size 700 nm, was used directly as catalyst in this kinetic study. Since it is difficult to vary the particle size of this catalyst for determining the internal diffusion resistance, numerical calculations were

carried out using the Weisz-Prater criterion to asses the influence of intra-particle diffusion resistances.[7] According to the Weisz-Prater criterion, the dimensionless parameter C_{wp} which represents the ratio of the intrinsic reaction rate to intra-particle diffusion rate, can be evaluated from the observed rate of reaction, the particle radius (R_p), effective diffusivity of limiting reactant (D_e) and concentration of reactant at the external surface of the particle (C_{AS}) that can be represented as:

$$C_{wp} = -r_{obs}\rho_p R_p^2 \Big/ D_e[C_{AS}] \qquad (5.1)$$

If $C_{wp} << 1$, then the reaction is intrinsically kinetically controlled.

If $C_{wp} >> 1$, then the reaction is limited by severe internal diffusion resistance.

The Diffusivity values (D) were calculated by using the Wilke-Chang equations.[8]

Effective diffusivity, D_e was calculated from the following correlation,

$$D_e = D_M \varepsilon \Big/ \tau \qquad (5.2)$$

where, ε and τ are the porosity and tortuosity of the Na-Y zeolite catalyst.

Molecular diffusivity, D_M was calculated from the following correlation,

$$D_M = \frac{7.4\times10^{-8} T(\chi M_W)^{1/2}}{\mu_l v_M^{0.6}} \qquad (5.3)$$

Where, χ, M_w, T, μ and v_m are the association factor of the solvent, molecular weight of solvent, temperature, viscosity of the liquid and molar volume of the solvent respectively. The diffusivity values calculated are presented in Table 5.2.

Table 5.2. Values of different parameters used in mass transfer analysis

Temperature, K	Observed rate, $r_{obs} \times 10^5$	$D_M \times 10^7$, * m^2/S	Porosity, ε	Tortuosity, τ	$D_e \times 10^8$, [a] m^2/S
393	8.6	1.43	0.3	3	1.43
413	20.6	1.7	0.3	3	1.7
433	40.6	2.14	0.3	3	2.14

[*]9.8 v/v % aniline, 7.2 v/v % EC and 83 v/v % triglyme, [a] These values of effective diffusivity obtained using the criterion is in similar range reported for liquid hydrocarbons in Na-Y zeolites.[9]

In the present case, the values of C_{WP} were calculated for aniline at temperatures 393, 413 and 433 K are 1.44×10^{-6}, 4.02×10^{-6} and 11.6×10^{-6} respectively, for the initial observed rates, which are very much less than 1. Therefore, it was concluded that there was no pore diffusion limitations in the Na-Y zeolite catalyst at the temperature range 393-433 K and the reaction was intrinsically kinetically controlled.

5.1.6. KINETIC MODEL

The analysis of initial rate data for *N*-alkylation of aniline by ethylene carbonate using Na-Y zeolite in triglyme indicates linear variation with aniline concentration and first order tending to zero order variation with ethylene carbonate concentration. Based on these observed trends, three different forms of rate equations were evaluated. Several basic assumption were made to develop the rate equations: (1) the rate of surface reaction is the rate limiting step for the *N*-alkylation; (2) adsorption and desorption rates are higher than the rate of surface reaction and (3) NPEA and CO_2 desorbed very fast from the catalyst surface keeping active sites free for the reaction. The following models were considered:

Model 1. Interaction of adsorbed ethylene carbonate species with the liquid phase aniline as rate limiting step (Eley-Rideal model).

The elementary steps for this Model can be written as follows;

$$EC + s \overset{K_A}{\rightleftharpoons} EC_s \qquad \text{(i)}$$

$$EC_s + An \xrightarrow{k_1} NPEA + CO_2 + s \qquad \text{(ii)}$$

Model 2. Both aniline and ethylene carbonate are adsorbed on Na-Y zeolite catalyst but adsorbed aniline do not react and the rate of adsorbed ethylene carbonate species with the liquid phase aniline is rate limiting step (Langmiur -Rideal model).

The elementary steps for this Model can be written as follows;

$$EC + s \overset{K_A}{\rightleftharpoons} EC_s \qquad \text{(i)}$$

$$An + s \overset{K_B}{\rightleftharpoons} An_s \qquad \text{(ii)}$$

$$EC_s + An \xrightarrow{k_1} NPEA + CO_2 + s \qquad \text{(iii)}$$

Model 3. Interaction of adsorbed ethylene carbonate species with adsorbed aniline species as rate limiting step (Langmiur-Hinselwood-Hougel-Watson model).

The elementary steps for this Model can be written as follows;

$$EC + s \overset{K_A}{\rightleftharpoons} EC_s \qquad \text{(i)}$$

$$An + s \overset{K_B}{\rightleftharpoons} An_s \qquad \text{(ii)}$$

$$EC_s + An_s \xrightarrow{k_1} NPEA + CO_2 + 2\,s \qquad \text{(iii)}$$

The rate equations were derived[10] for these models and are presented in Table 5.3. In order to check the applicability of the rate models derived under isothermal and

integral conditions, a semi batch reactor model was developed. Material balance of the liquid phase components based on Model 2 is given bellow as an example:

$$\frac{dC_{An}}{dt} = -R_1 = -\frac{kwC_{AN}C_{EC}}{1 + K_A C_{EC} + K_B C_{AN}} \tag{5.4}$$

$$\frac{dC_{EC}}{dt} = -R_1 = -\frac{kwC_{AN}C_{EC}}{1 + K_A C_{EC} + K_B C_{AN}} \tag{5.5}$$

$$\frac{dC_{NPEA}}{dt} = R_1 = \frac{kwC_{AN}C_{EC}}{1 + K_A C_{EC} + K_B C_{AN}} \tag{5.6}$$

With the initial conditions:

$at, t = 0, C_{An} = C_{An,0}, C_{EC} = C_{EC,0}, C_{NPEA} = 0$

Where, R_1 is the reaction rate, Kmol/m^3/s; C_{AN}, C_{EC}, and C_{NPEA} are the concentration of aniline, ethylene carbonate and *N*-phenyl ethanolamine respectively in Kmol/m^3; $C_{AN,\,0}$ and $C_{EC,\,0}$ are the initial concentration of aniline and ethylene carbonate respectively in Kmol/m^3; w, concentration of catalyst, Kg/m^3; k , reaction rate constant, m^6/ Kg.Kmol.s, where, $k = k_1 \times K_A$; k_1, surface reaction rate constant, m^3/Kg.s and K_A, K_B are the adsorption constants for ethylene carbonate and aniline respectively in m^3/Kmol.

In order to select an appropriate rate equation, a non-linear least square regression analysis method was used for each rate equation to get the best-fit values of the parameter. For this purpose an optimization programme based on Marquardt's algorithm combined with Runge-Kutta method was used. The optimization method involved an objective function Φ_{min}, the value of which minimized during the optimization and defined as:

$$\phi_{\min} = \sum_{i=1}^{4} \sum_{i=1}^{n} \left(Yi_{\exp} - Yi_{\mathrm{mod}} \right) \tag{5.7}$$

where, Yi_{exp} and Yi_{mod} represent experimental and predicted concentration of ith species and n represents the number of samples. The mean average of relative residuals (% RR) was also calculated based on the following expression:

$$\%RR = \sum_{i=1}^{4} \sum_{i=1}^{n} \frac{(Yi_{\exp} - Yi_{\mathrm{mod}})}{Yi_{\exp}} \times 100 \tag{5.8}$$

Table 5.3. Comparison of various models for *N*-alkylation of aniline by ethylene carbonate to *N*-phenyl ethanolamine using Na-Y zeolite as catalyst

Model	T, K	$k_1 \times 10^5$	K_A	K_B	% RR	Φ_{min}
$R_A = \frac{kwC_{AN}C_{EC}}{1+K_AC_{EC}}$	393	1.80	1.327	-	± 5.7	1.06×10^{-7}
	413	5.75	1.353	-	± 7.2	4.3×10^{-9}
(**1**)	433	19.4	1.129	-	± 7.5	3.24×10^{-12}
$R_A = \frac{kwC_{AN}C_{EC}}{1+K_AC_{EC}+K_BC_{AN}}$	393	1.84	1.424	0.30	± 3.8	4.2×10^{-16}
	413	6.19	1.349	0.209	± 2.4	1.94×10^{-18}
(**2**)	433	19.4	1.132	0.099	± 6.3	3.2×10^{-16}
$R_A = \frac{kw^2C_{AN}C_{EC}}{\{1+K_AC_{EC}+K_BC_{AN}\}^2}$	393	2.69	0.964	0.1	± 2.5	1.4×10^{-8}
	413	57.1	0.538	-0.22	± 9.1	6.28×10^{-4}
(**3**)	433	245	0.582	0.004	± 17.7	4.3×10^{-3}

The rate models were discriminated based on the Φ_{min} and % RR values obtained by regression analysis for each model. In addition, the thermodynamic criteria proposed by Vannice et al.[11] and Boudart[12] were also considered for goodness of fit for the present model. These criteria are; (i) rate constants and adsorption constants should be positive ($k > 0$, $K > 0$) and (ii) activation energy should be positive ($Ea > 0$). The values of Φ_{min}

and % RR along with the optimized rate and adsorption parameters are presented in Table 5.3. The main objective here was not only to discriminate models, but to show the significance of aniline interaction with electrostatic environment in zeolites cage (adsorption constants) for reaction occurring in zeolites cage.

Out of the three models, based on above criteria, Model-3 was rejected because it gave negative values for the constant K_B at 413 K. Among the remaining models, Model- 2 has the lowest Φ_{min} and % RR. Hence, the model represents the kinetic of *N*-alkylation of aniline by ethylene carbonate in the range of operating conditions mentioned in Table 5.2. A few experimental and predicted concentration-time profiles are shown in Figures 5.13 – 5.15 which showed a good agreement between the experimental and theoretical data points and % RR values are in the range of ±2-6. This indicated the stability of the model. It may be noted here that the value of $K_B\ C_{AN}$ is maximum 0.32, which is not significantly affecting the denominator of Model 2. Hence, the denominator value of Model 1 and Model 2 are not significantly different. Therefore, initial rates and concentration - time profiles predicted by these models are almost similar. The advantage of Model 2 is that it accounts for a weak interaction of aniline with zeolite in the pores.

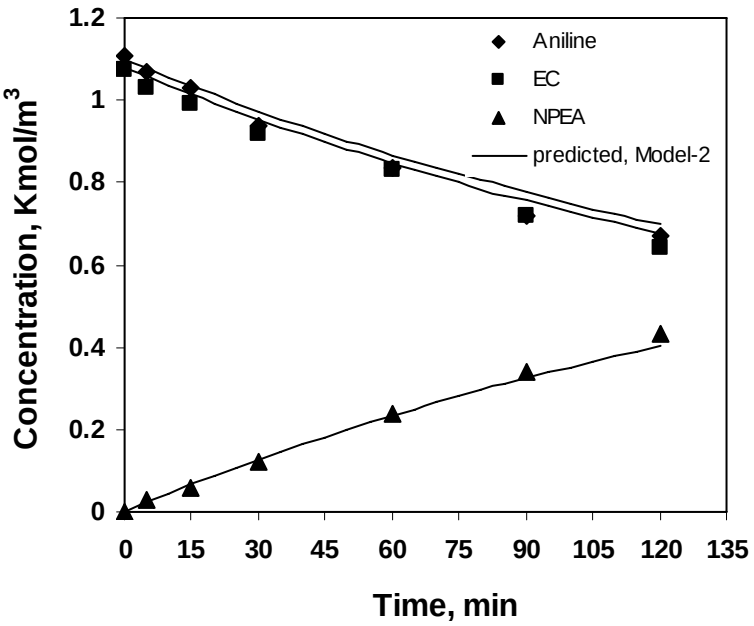


Figure 5.13. Concentration-Time profile at 393 K

Reaction conditions: aniline, 1.075 Kmol/m^3; ethylene carbonate, 1.075 Kmol/m^3; Na-Y catalyst, 10 Kg/m^3; Triglyme(solvent), 0.223 Kmol/m^3; N_2 atmosphere; Time, 2 h; Agitation speed, 13.3 Hz; Total volume, 10 ml.

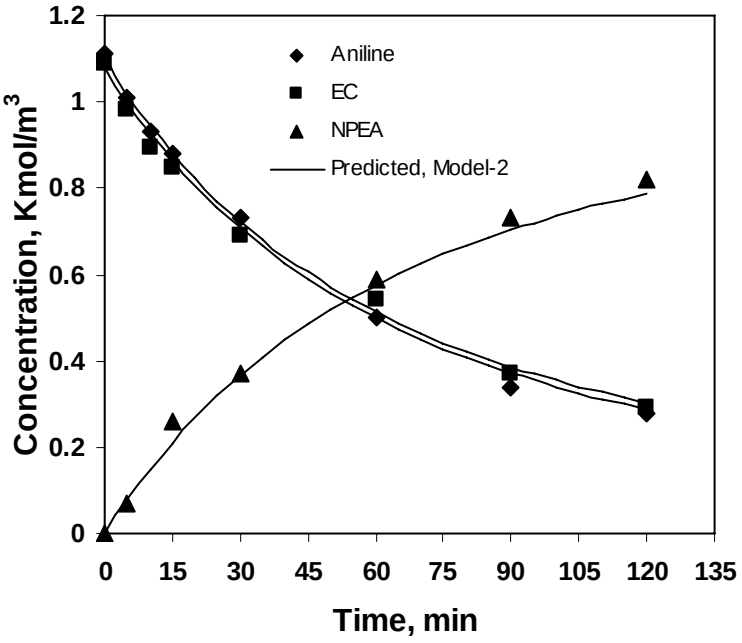


Figure 5.14. Concentration-Time profile at 413 K

Reaction conditions: aniline, 1.075 Kmol/m^3; ethylene carbonate, 1.075 Kmol/m^3; Na-Y catalyst, 10 Kg/m^3; Triglyme(solvent), 0.223 Kmol/m^3; N_2 atmosphere; Time, 2 h; Agitation speed, 13.3 Hz; Total volume, 10 ml.

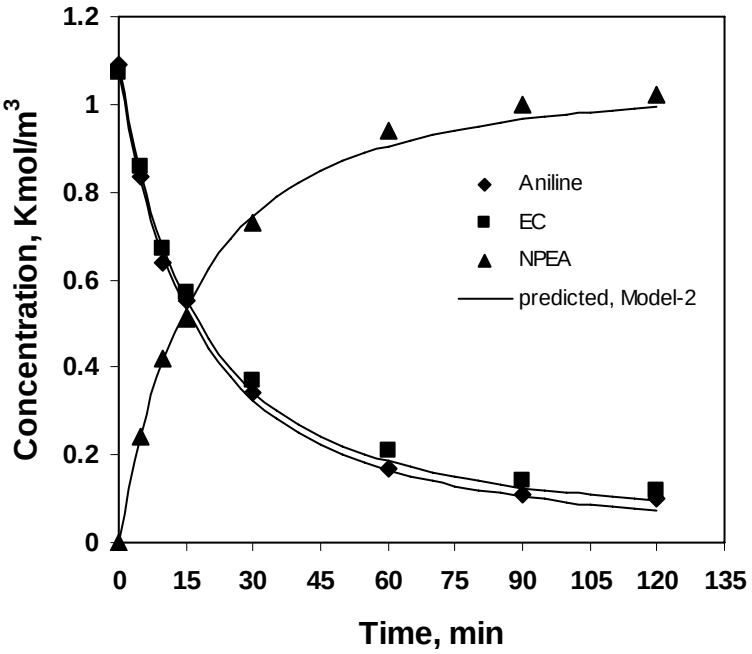


Figure 5.15. Concentration-Time profile at 433 K

Reaction conditions: aniline, 1.075 Kmol/m^3; ethylene carbonate, 1.075 Kmol/m^3; Na-Y catalyst, 10 Kg/m^3; Triglyme(solvent), 0.223 Kmol/m^3; N_2 atmosphere; Time, 2 h; Agitation speed, 13.3 Hz; Total volume, 10 ml.

From the temperature dependence of rate parameters (Figure 5.16) the activation energy of the reaction was calculated to be 83.11 KJ/mol, which showed the reaction was kinetically controlled and gave another proof of absence of intra-particle diffusion resistance. Finally it may be noted that the model selected is representing the experimental data adequately, however, since no attempts has been made here to rigorously discriminate rival models, the possibility of other models representing the data equally well can not be ruled out at this stage.

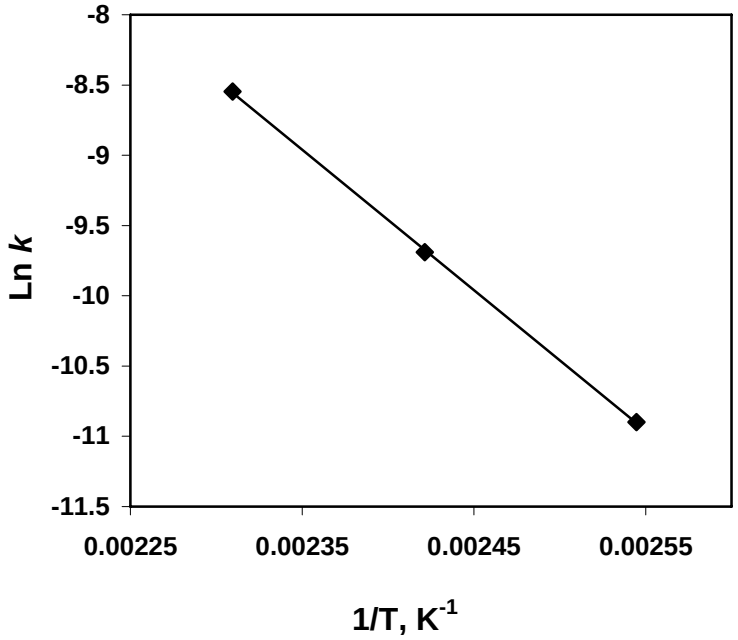


Figure 5.16. Temperature dependence of rate constant

5.1.7. CONCLUSION

Kinetics of *N*-alkylation of aniline by ethylene carbonate using a Na-Y zeolite as catalyst was studied in a batch reactor in the temperature range of 393-433 K. The reaction was found to be first order with respect to aniline concentration and first order tending to zero order with respect to ethylene carbonate concentration. A rate equation was derived using a catalytic cycle based on molecular level description of elementary steps and assuming adsorption of ethylene carbonate on Na-Y zeolite catalyst followed by reaction with aniline as the rate determining step. The kinetic parameters were estimated using non-linear regression analysis and activation energy was evaluated (83.1 KJ/mol).

Notations

An	aniline
EC	ethylene carbonate
NPEA	*N*-phenyl ethanolamine
C_{An}	concentration of aniline, Kmol/m^3
C_{EC}	concentration of ethylene carbonate, Kmol/m^3
C_{NPEA}	concentration of *N*-phenyl ethanolamine, Kmol/m^3
C_{wp}	Wiesz-Prater criterian
$C_{An,\,0}$	initial concentration of aniline, Kmol/m^3
$C_{EC,\,0}$	initial concentration of ethylene carbonate, Kmol/m^3
D_e	effective diffusivity, m^2/s
D_M	molecular diffusivity, m^2/s
d_p	particle diameter, m
k	reaction rate constant, m^6/Kg.Kmol.s (defined by Model 1 and 2, where $k = k_1 \times K_A$); m^6/Kg.Kmol.s (defined by Model 3, where $k = k_1 \times K_A \times K_B$)
k_1	Surface reaction rate constant, m^3/Kg.s (defined by Model 1 and 2) Kmol.m^3/Kg^2.s (defined by Model 3)
K_A	adsorption constant for ethylene carbonate, m^3/Kmol
K_B	adsorption constant for aniline, m^3/Kmol
R_A	initial rate of aniline, Kmol/m^3/s
R_1	rate of reaction, Kmol/m^3/s
R_p	particle, radius, m
s	catalyst surface
T	temperature, K
w	catalyst loading, Kg/m^3

Greek letters,

χ	association factor of the solvent
ε	porosity of catalyst
ϵ	dielectric constant
Φ_{min}	Parameter defined by equation 5.7
μ_l	viscosity of the liquid
v_m	molar volume of the solvent
τ	tortuosity of the catalyst
ρ_p	density of particle

PART II

5.2. SYNTHESIS OF β-AMINO ALCOHOLS FROM ANILINE AND ETHYLENE CARBONATE: MECHANISTIC STUDIES USING *IN SITU* FTIR TECHNIQUE

5.2.1. INTRODUCTION

β-amino alcohol is an important class of compound and its synthesis via *N*-alkylation of anilines by alkylene carbonate is simple and useful reaction but it is not investigated through mechanistic point of view. The conventional pre-and post-reaction investigations through physico-chemical characterization contribute to some extent to understanding of the reaction. However, most often they do not adequately reflect the events that occur on the system under actual reaction conditions, like short-lived intermediates, surface complexes and the reaction mechanism. The *in situ* characterization techniques help to understand the interaction of adsorbed species with catalyst surface and highlight the chemical and orientational changes of the adsorbate, short-lived intermediates and surface complexes that are formed during the reaction, which in turn provide information about the reaction mechanism. In addition, *in situ* techniques throw light on how catalytic conversion and product selectivity depend on the structural and electronic properties of the catalyst and the mode of catalyst deactivation.

Among the various techniques that are used to study catalytic process, infrared spectroscopy (IR) plays an important role. This is primarily due to fact that IR provides actual information on the structure, geometry and orientation of practically all molecules that are present in a reaction mixture, irrespective of the physical state, temperature or pressure. IR is, therefore, a feasible tool not only for the characterization of reactants and

products, but also of catalytically active sites, support materials, ligands, promoters and intermediates of homogeneous and heterogeneous catalysts. A review on application of IR spectroscopy in catalysis by Ryczkowski demonstrates the various important applications of FTIR specially in understanding various catalytic processes.[13]

In the literature, various kind of interaction and the adsorption site of the molecules like: benzene,[14] pyridine,[15] 2,6-dimethyl pyridine,[15] H_2S,[15] CO,[16] N_2[16] and boric acid trimethyl ester (BATE)[17] etc. in the zeolite Y were investigated using FTIR spectroscopy to show that Na^+ cations present only in S_{II} position (Figure 5.18) are accessible to the guest molecules for catalytic reactions as well as to determine the nature and strength of acidity and basicity. Gomez and Anunziata have studied the aniline adsorption on Na-Y[18a] and MCM-41[18b] using FTIR spectroscopy and they have demonstrated that aniline binds strongly with Na-Y through unpaired electrons of amino groups and Na^+ of the zeolites whereas it interacts through π bonding of aromatic ring with structural Si-OH groups of MCM-41. Sorption of anilines by montmorillonite saturated with various cations was investigated by Yariv et al.[19] to identify the various interactions between aniline and adsorption sites in the interlayer space of the clays. Singh et al.[20] have also studied the interaction of aniline and *N*-methyl aniline with zeolites (H-Beta and H-Y) by FTIR spectroscopy which revel that hydroxyl groups of zeolites interacts with both π electrons of aromatic ring as well as lone pair of electrons of amines. Vijayraj et al.[21] have investigated the mechanism of *N*-methylation of aniline with methanol on Cu_1-ZnxFe_2O_4 catalyst using DRIFTS study.

Beutel[22] and Bonino et al.[23] have studied the interaction of dimethyl carbonate in the pores of Na-X and Na-Y zeolite respectively using IR spectroscopy. From the

literature it is clear that there is no information on the interaction of ethylene carbonate with any adsorbate as well as there are no previous reports on mechanistic studies of *N*-alkylation of aniline by ethylene carbonate. In this work, a detailed vapor phase interaction of aniline and ethylene carbonate on Na-Y for production of *N*-phenyl ethanolamine using *in situ* FTIR technique (DRIFT) was investigated and based on these results, reaction mechanism was proposed.

5.2.2. EXPERIMENTAL

Aniline was purchased from M/S S.D. fine chemicals, India and ethylene carbonate (EC) from Aldrich chemicals, USA. Na-Y zeolite was provided by Süd-Chemie, India and was characterized by XRD analysis (see Chapter 4, Section on Spectra, page no. 226). *In situ* FTIR studies were carried out using Shimadzu FTIR spectrometer (SSU8300) using diffuse reflectance infrared Fourier transform (DRIFT) technique, equipped with MCT-A detector. A cross-sectional view of diffuse reflection cell is shown in Figure 5.17.

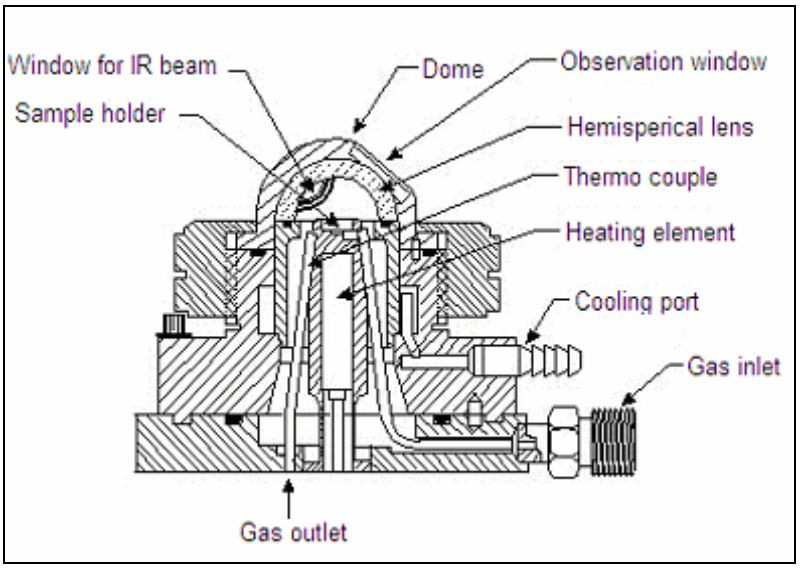


Figure 5.17. Cross-sectional view of diffuse reflection cell

5.2.2.1. Experimental procedure for determination of nature of acidity

Nature of acidity of the Na-Y zeolite was determined by pyridine adsorption. The fine powder of Na-Y catalyst was placed in the DRIFT cell and heated to 673 K in flow of inert gas (N_2) for 4 h. It was cooled to 373 K under inert atmosphere and then pyridine was adsorbed on the catalyst in N_2 flow. The physisorbed pyridine was removed by flushing the cell with N_2 for 45 min at the same temperature and the spectrum was recorded. The temperature dependant desorption of pyridine was carried out at 373 K, 473 K and 673 K. The spectrum of the neat catalyst (before pyridine adsorption) at 373 K was subtracted from all the spectra.

5.2.2.2. Experimental procedure for *in situ* FTIR spectroscopic studies

The catalyst Na-Y zeolite was freshly calcined *in situ* at 673 K for 4 h to remove moisture adsorbed on the catalyst surface in the DRIFT sample holder under nitrogen flow. The catalyst was cooled to 443 K and 10 μl of desired compound or reaction mixture was introduced in the N_2 flow and IR spectra were recorded at different temperatures in the range 443 K to 523 K. In the first experiment, aniline was injected in the beginning at 443 K in N_2 stream. Physisorbed aniline was removed by flushing the cell with N_2 for 45 min. The chemisorbed aniline was analyzed and when there was no further decrease in the intensity of aniline peaks, 10 μl ethylene carbonate was injected. The spectra were recorded as function of time. In the second experiment, ethylene carbonate was injected initially on freshly calcined catalyst at 443 K. After removing the physisorbed ethylene carbonate by flushing the system with N_2 for 1 h, aniline was injected. The spectra were recorded as a function of time, again EC was injected and spectra were recorded as a function of time. In third experiment a 1:1 mixture of aniline

and ethylene carbonate was injected on freshly calcined catalyst at 443 K and the spectra were recorded as a function of time. In the fourth experiment 1:1 mixture of aniline and ethylene carbonate was injected on freshly calcined 4A catalyst at 443 K and spectra were recorded as a function of time. The spectrum of neat catalyst at 443 K was subtracted from all the spectra. All the spectra presented here are as the difference spectra between molecules absorbed on the Na-Y zeolite and virgin Na-Y zeolites at 443 K.

5.2.3. RESULTS AND DISCUSSION

In the present work, interaction of aniline and ethylene carbonate with Na-Y zeolite to form β-amino alcohol was investigated in details by *in situ* IR spectroscopy using DRIFT technique and based on the results the mechanism for the formation of NPEA from aniline and ethylene carbonate on Na-Y is proposed.

The optical phenomenon known as diffuse reflectance is commonly used in UV-Vis, NIR and MIR regions to obtain molecular spectroscopic information.[24] When it is applied in MIR area with a Fourier transform, it is known as diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS). It is usually used to obtain the spectra of powders with minimum sample preparations. The collection and analysis of the surface-reflected electromagnetic radiation as a function of frequency or wavelength obtain a reflectance spectrum.

5.2.3.1. Determination of acidic sites on Na-Y zeolite

The Y faujasite has a cubic structure with space group $Fd\bar{3}m$ and it has 24.85 to 24.61 Å unit cell parameter.[25] One unit cell contains eight sodalite cages (beta cage, 8 Å of diameter) and eight super cages (alpha cages, 12.5 to 19 Å of diameter, depending on

if it is Na or H form respectively). Its pore system is relatively spacious and its super cages of a diameter of 12.5 Å connected tetrahedrally with four neighboring cages through windows with a diameter of 8 Å formed by 12 TO_4 tetrahedra. Zeolite Y is therefore classified to posses a three dimensional, a 12 membered-ring pore system. General formula for Na-Y zeolites can be given as $Na_{57}(AlO_2)_{57}(SiO_2)_{135}$ and structure of Na-Y zeolite is shown in Figure 5.18. When Y zeolites are in the Na-Y form, the Na^+ cations occupy S_I, $S_{I'}$ and S_{II} sites. The S_I, $S_{I'}$ sites are located in the hexagonal prisms and the sodalite cages respectively where they are not accessible at low temperatures even for small molecules such as N_2 and CO.[16] The only accessible Na^+ cations are in S_{II} positions in six ring windows where they are coordinated to the three framework oxygen anions to form regular triangle.

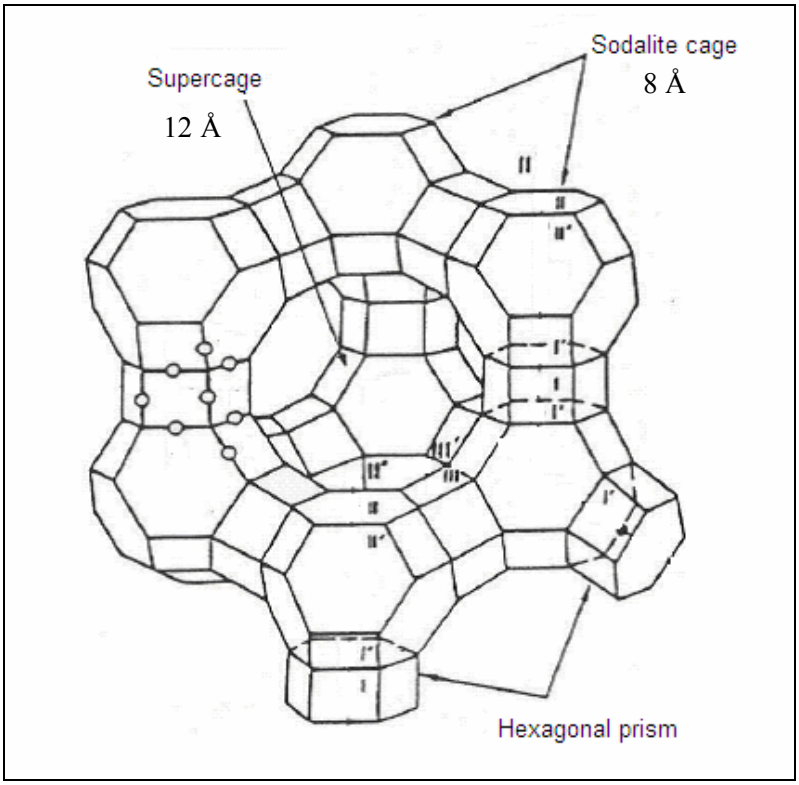


Figure5.18. Structure of Na-Y zeolite

Nature of acidity of the Na-Y zeolite was determined by pyridine adsorption. The spectra of adsorbed pyridine on Na-Y (Figure 5.19) showed a band at 1442 cm^{-1} confirming presence of Lewis acid sites. Absence of band at 1540 cm^{-1} confirms the lack of Bronsted acidity, which is in agreement with the lack of zeolitic –OH groups. Bands at 1442 and 1593 cm^{-1} are specific of the ν_{19b} and ν_{8a} vibration mode ($\nu_{CC(N)}$) of pyridine interacting with weak Lewis acidity.[26] The band at 1442 and 1577 cm^{-1} are due to the combined C-C stretching and in plane C-H bending modes of pyridine. These coordination sites are attributed to the Na^{+} centre. Pyridine adsorbed on base exchanged aluminosilicates shows that base totally eliminates Brønsted acidity from aluminosilicates which originally posses both Lewis as well as Brønsted acidity. It was also shown that total amount of chemisorbed pyridine on base exchanged aluminosilicates was less than aluminosilicate which was a proof for acidity poisoning effect of base metals.

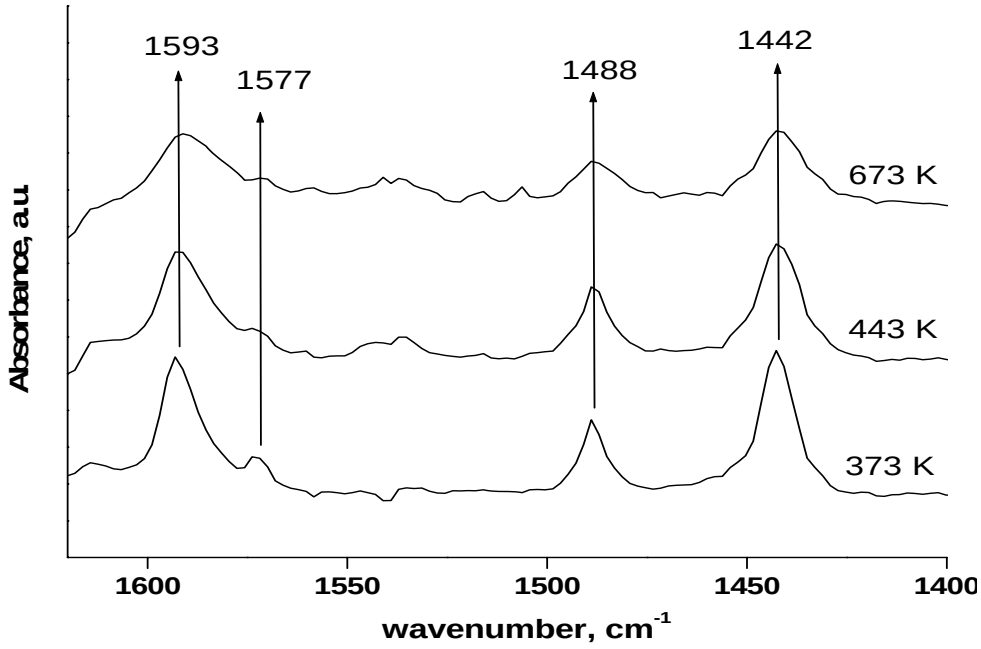


Figure 5.19. FTIR spectra of temperature programmed desorption of Pyridine on Na-Y zeolite

5.2.3.2. Adsorption of aniline on Na-Y catalyst

To study the interaction of aniline with catalyst surface during the reaction, aniline was adsorbed on freshly activated Na-Y zeolite. Aniline was adsorbed on catalyst surface at temperature, 443 K and spectra were recorded at different temperatures as a function of time. The spectra clearly show activation of aniline on Na-Y (Figure 5.20 A and B). Large shift in the N-H asymmetric and symmetric stretching frequencies to lower frequencies to 3367 and 3308 cm^{-1} respectively[21] compared to 3450 and 3390 cm^{-1} in neat aniline[27] indicate weakening of N-H bond to much greater extent (Figure 5.20 A). Appearance of broad band at 3620 cm^{-1} indicates the formation of OH bond due to the interaction of N-H proton with zeolite oxygen forming surface hydroxyl groups. This clearly showed the activation of aniline on Lewis acid sites of the catalyst. A series of low intensity bands at 1949, 1851, 1787 and 1722 cm^{-1} attributed to out of plane aromatic C-H bending vibrations (νC-H) indicated less interaction of aromatic ring with Na-Y zeolite (Figure 5.20 B).[28] One band at 1625 cm^{-1} and two strong bands at 1597 and 1498 cm^{-1} are assigned to NH_2 bending[27] and C=C stretching vibration of phenyl ring[27] (ν16a and ν13a) respectively, which are not shifted to great extent compared much from the pure aniline. The peaks for adsorbed aniline still existed at 523 K, which indicated that aniline was strongly bonded to Na-Y zeolite. It is probable that most of the adsorbed aniline interact with microporous material through lone pair of electrons of the amino group and sodium cations (Na^+).[18a]

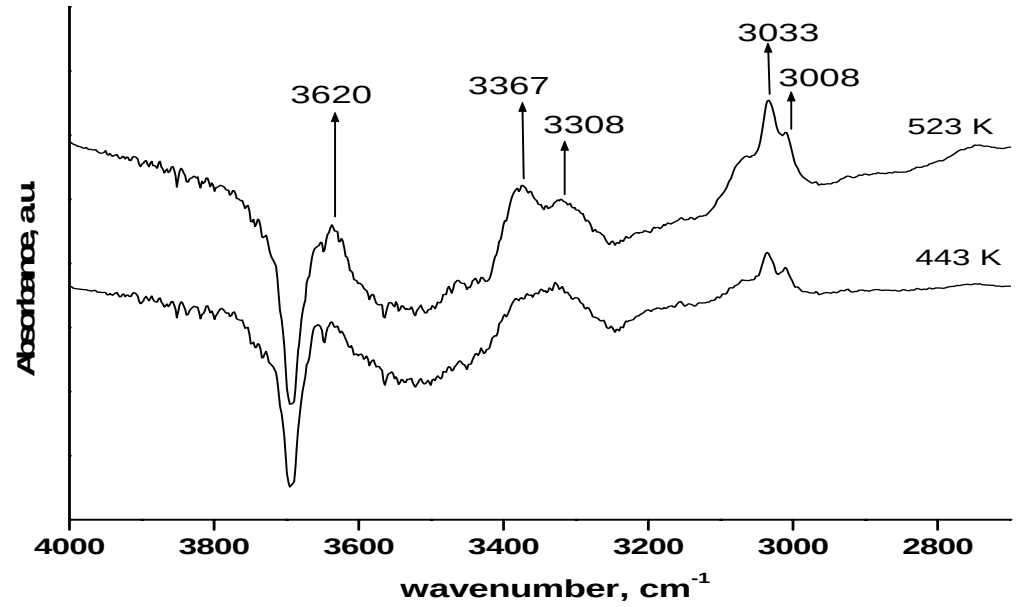


Figure 5.20 A. FTIR spectra of temperature programmed desorption of aniline on Na-Y zeolite (4000-2700 cm^{-1})

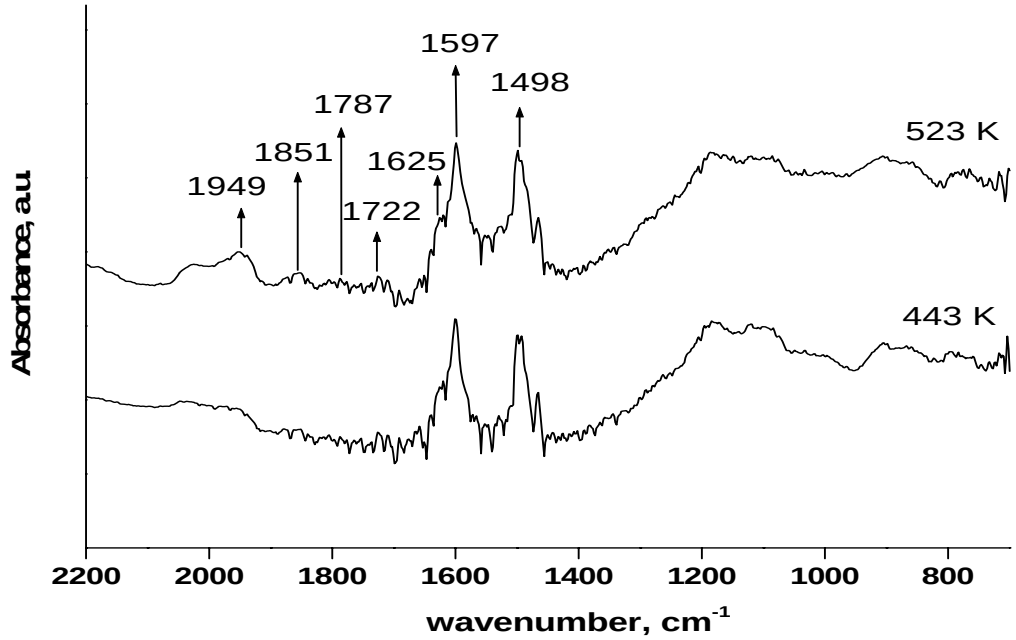


Figure 5.20 B. FTIR spectra of temperature programmed desorption of aniline on Na-Y zeolite (2200-700 cm^{-1})

5.2.3.3. Sequential adsorption of aniline and ethylene carbonate

The interaction of ethylene carbonate (EC) with activated aniline was studied. Initially aniline was introduced on Na-Y at 443 K followed by injection of ethylene carbonate (Figure 5.21). Immediately after the EC reached the catalyst surface, instantaneous reaction of ethylene carbonate with activated aniline was observed with liberation of CO_2 at 2341 cm^{-1}. Increase in the intensity of CO_2 peak with time and nonobservance of doublet at 1774 and 1800 cm^{-1} corresponding to ethylene carbonate C=O clearly confirms the reaction of ethylene carbonate with activated aniline (Figure 5.22 A). The spectrum recorded after 10 minutes shows the peaks corresponding to product *N*-phenyl ethanolamine. For reference, the spectrum of NPEA from Aldrich FTIR database is given in the Figure 5.21.[29] NPEA peaks, which are not interfering with aniline or ethylene carbonate are seen at 3394 cm^{-1} corresponding to alcoholic –OH group and a broad multiplet at 871 cm^{-1} corresponding to OH deformation. Peak at 2941 cm^{-1} can be assigned to aliphatic CH_2 stretching bands of NPEA. Intensity of the NPEA and CO_2 peaks increases with time indicating formation of NPEA by reaction of ethylene carbonate.

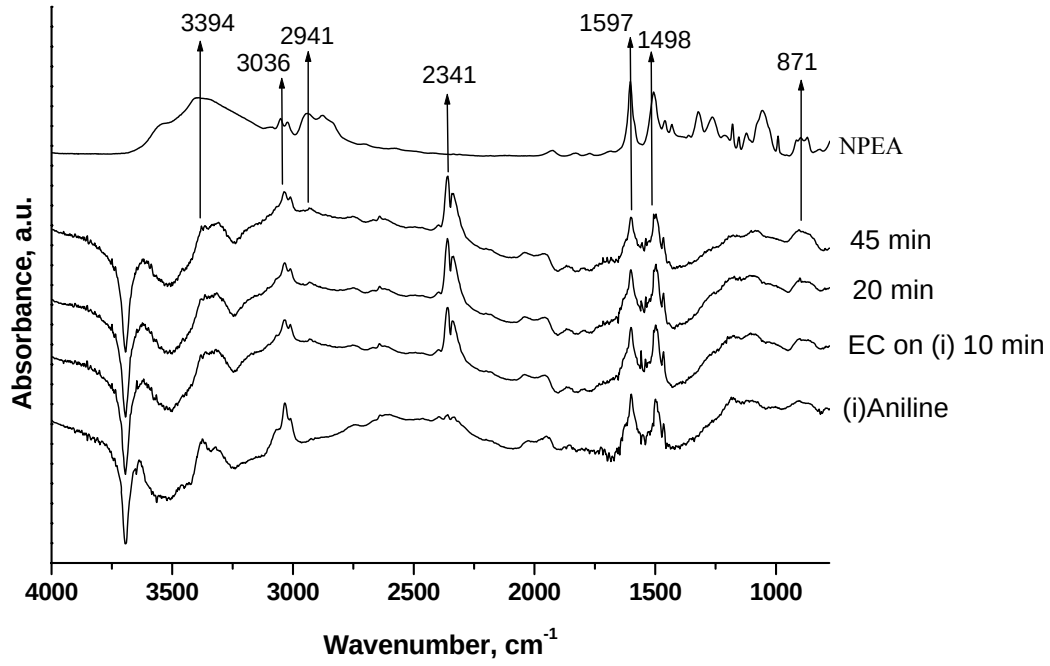


Figure 5.21. FTIR spectra of sequential adsorption of aniline and ethylene carbonate on Na-Y

5.2.3.4. Adsorption of ethylene carbonate on Na-Y catalyst

When ethylene carbonate was injected on catalyst surface, it was observed that there was no significant change in peaks position of adsorbed ethylene carbonate compared to neat ethylene carbonate (Figure 5.22 A and B). The C=O stretching vibration of adsorbed ethylene carbonate appears as doublet at 1800 and 1774 cm^{-1} compared to 1801 and 1774 cm^{-1} for liquid EC (Figure 5.22 A).[30] The frequencies corresponding to EC ring vibration and the ring breathing vibration are observed at 1146 cm^{-1} and 893 cm^{-1} respectively (Figure 5.22 B). Whereas, the corresponding bands for liquid EC are reported at 1155 and 894 cm^{-1} respectively. This showed physisorption of EC on Na-Y. When temperature programmed desorption of EC was monitored as a function of time (Figure 5.22 A and B), it was clearly seen that with time and at higher temperature (443 K at 30 min, and 523 K at 5 & 20 min) the intensity of all the ethylene

carbonate peaks decreased gradually. This gives clear evidence for physisorption of EC on Na-Y. Before complete desorption of EC, aniline was injected to test if aniline reacts with physisorbed EC, however no reaction between aniline and physisorbed EC was observed on Na-Y (Figure 5.23). It proves that physisorbed EC and aniline do not interact with each other for further reaction. This may be due to the adsorption of aniline on the sites, which are isolated from physisorbed EC which did not allow reaction of aniline with pre-adsorbed EC. However when again EC was injected followed by aniline, formation of CO_2 was observed (Figure 5.23) confirming the reaction of EC with activated aniline. This may indicate that EC molecule reacts with activated aniline without sitting on the catalyst surface. Beutel has studied the alkylation of phenol with dimethyl carbonate (DMC) using Na-X zeolite by FTIR spectroscopy.[22] Interaction of DMC with Na-X[22] and Na-Y[23] shows two possible adsorption modes of DMC inside the supercage of these zeolites. In first mode there is an interaction of carbonyl carbon with Na^+ ion. However this type of interaction is observed only at room temperature. At higher temperature second type of interaction is observed where the formation of bidentate complex in which ester oxygen atoms of DMC chelates one Na^+ ion is observed. The later bonding has led to alkyl cleavage of DMC at elevated temperature yielding monomethyl carbonate and cleaved methyl group reacts with zeolitic oxygen forming methoxy group. However it is not possible for ethylene carbonate to form bidentate complex with Na^+ in the supercage of Na-Y due to rigid ring structure of ethylene carbonate. Because of which the activation of EC leading to liberation of CO_2 in the supercage of Na-Y is not possible.

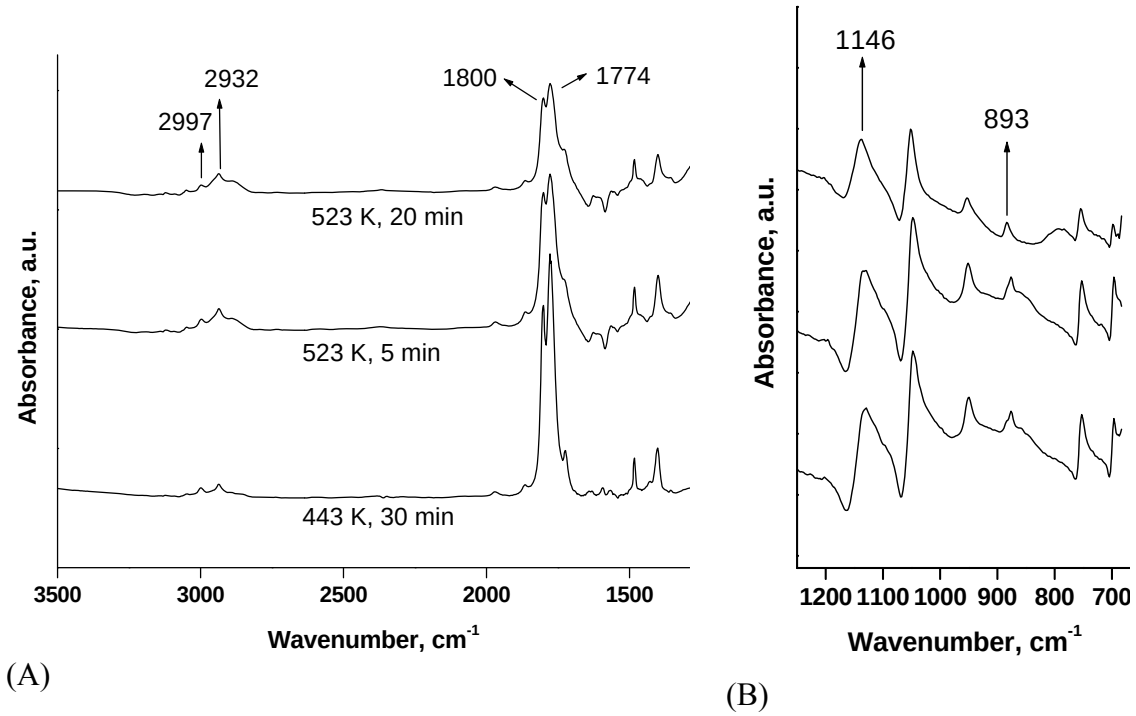


Figure 5.22. FTIR spectra of temperature programmed desorption of ethylene carbonate on Na-Y zeolite

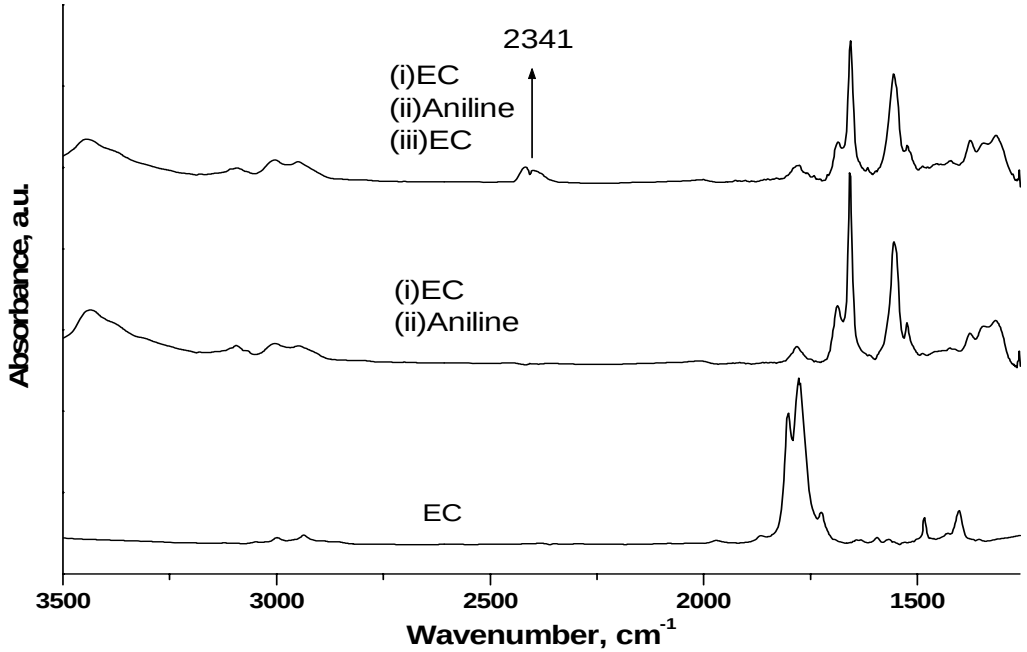


Figure 5.23. FTIR spectra of sequential adsorption of ethylene carbonate, aniline and ethylene carbonate on Na-Y

5.2.3.5. Adsorption of 1:1 mixture of aniline and ethylene carbonate

To check the sequence of activation of both the reactants, 1:1 mixture of aniline and ethylene carbonate was injected at 443 K. Instantaneous reaction of aniline with ethylene carbonate was observed with liberation of CO_2 (Figure 5.24). In the spectra, peaks corresponding to activated aniline and NPEA formation were clearly seen and no peaks corresponding to ethylene carbonate were observed.

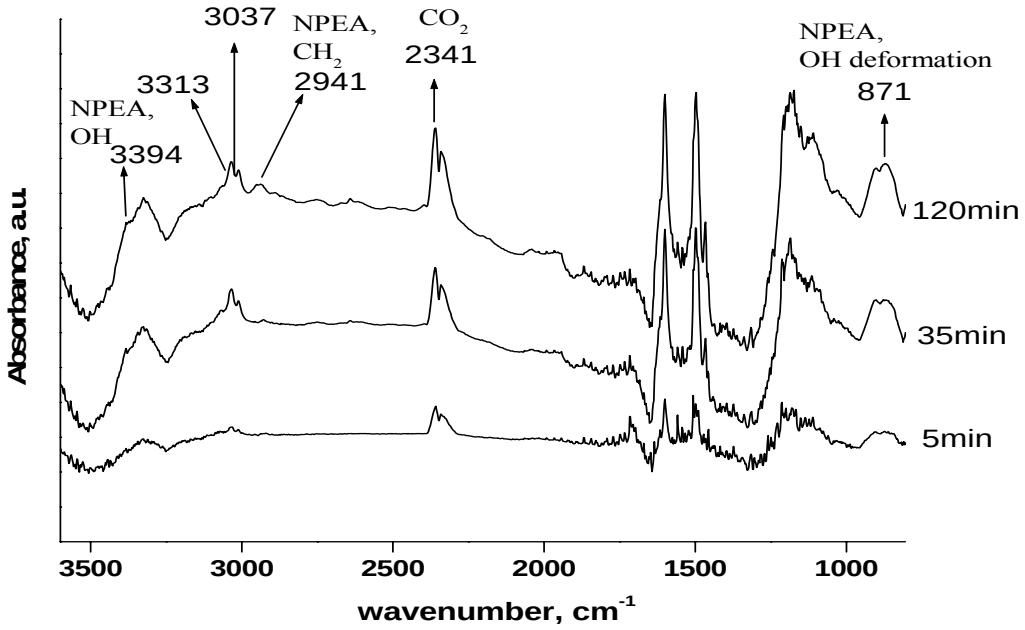


Figure 5.24. Time-dependant FTIR spectra of adsorption of 1:1 mixture of aniline ethylene carbonate on Na-Y catalyst at 443 K

5.2.3.6. Adsorption of aniline and ethylene carbonate on 4A catalyst

To reconfirm that reaction takes place in the supercage of Na-Y and not on the surface of the catalyst, reaction of aniline with EC was carried out using 4A as catalyst. Zeolite 4A is known to have weak surface Lewis acidity[31] and the pore size is 4 Å, which is smaller than aniline (5.4 Å). Surface characteristics of 4A and Na-Y would be same (aluminosilicate) as the cation in case of Na-Y is located only in the cages or pores of the

zeolite and hence there is no cation present on the surface of the Na-Y. If reaction of aniline and EC would take place on the surface of Na-Y then it is expected that 4A also catalyze the same reaction. The main source of acidity in case of Na-Y is the Na^+ cation, which is located in the cages of the zeolite and activates aniline that in turn causes the reaction with EC to yield NPEA. To test if aniline and/or EC get activated on the surface of 4A, aniline and EC were injected on the surface of catalyst 4A (Figure 5.25). In the first experiment, aniline was injected and it was observed that there was no interaction of aniline with 4A. In the second experiment, ethylene carbonate was injected after injection of aniline and it was observed that no interaction of EC with 4A and no peaks corresponding to NPEA indicating only physisorption of aniline and EC without activation on the catalyst surface. This was reconfirmed in the third experiment where mixture of aniline and EC was injected and still no formation of NPEA was observed in FTIR spectrum. These experiments clearly showed that *N*-alkylation of aniline by ethylene carbonate took place in the pores of Na-Y and not on the surface.

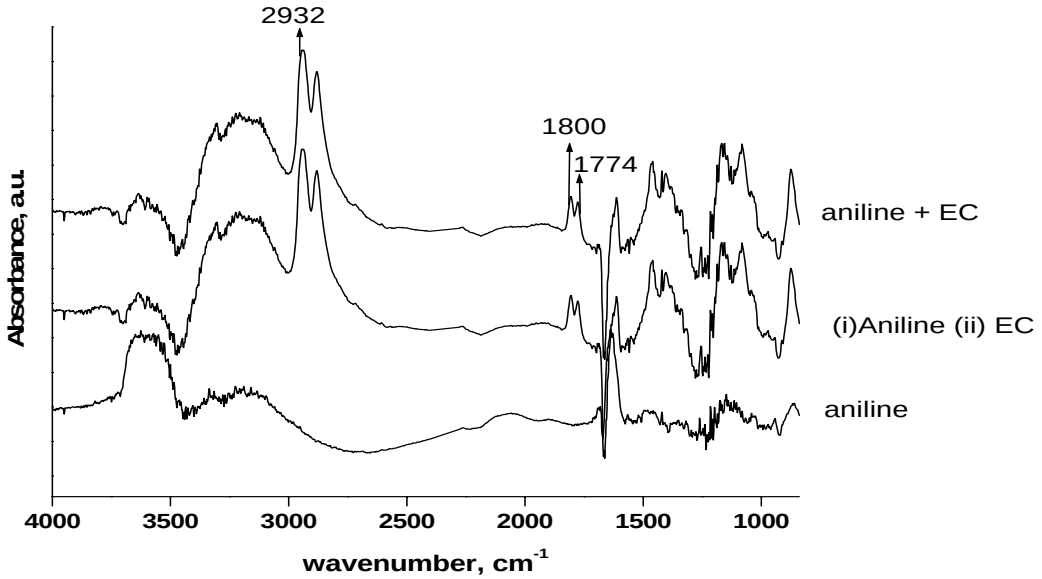
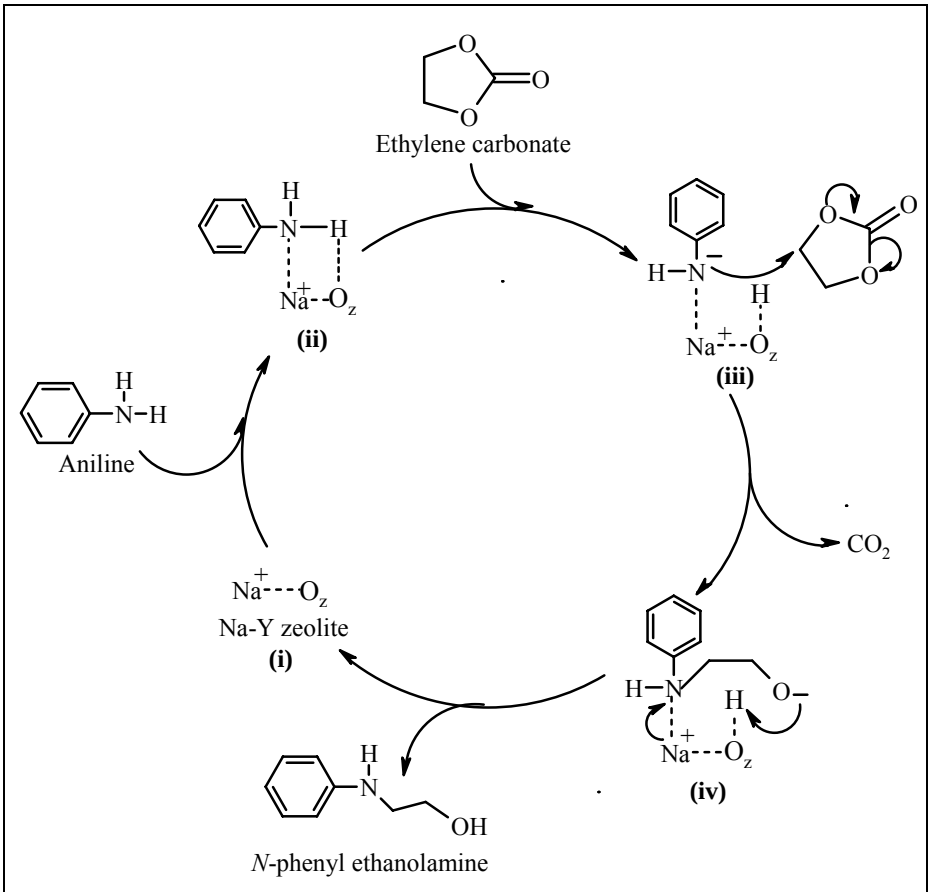


Figure 5.25. FTIR spectra of sequential adsorption of aniline, ethylene carbonate and aniline on 4 A

5.2.3.7. Reaction mechanism

Based on the above *in situ* experiments, the following mechanism for the reaction of aniline and ethylene carbonate using Na-Y catalyst was proposed (Scheme 5.3). In the catalytic cycle, first aniline gets activated on the Lewis acid sites of Na-Y i.e. Na^+ forming partial negative charge on nitrogen atom of aniline leading to the formation of nucleophile species (ii). During this activation, N-H proton interacts with zeolitic oxygen atom forming surface hydroxyl group species (iii). In the second step nucleophilic attack of NH^- on methylene carbon of ethylene carbonate results in liberation of CO_2. In the third step O^- of the adsorbed product species (iv) abstracts the proton from the surface hydroxyl group to give *N*-phenyl ethanolamine.



Scheme 5.3. Proposed catalytic cycle for β-amino alcohol synthesis

5.2.4. CONCLUSION

Mechanistic studies of *N*-alkylation of aniline by ethylene carbonate using Na-Y catalyst was also studied by *in situ* FTIR technique. The *insitu* FTIR study showed that aniline activation on cationic Lewis acid sites of Na-Y i.e. Na^+ was the first step in this reaction, however ethylene carbonate did not get activated on the catalyst. The activated aniline acted as nucleophile and reacted instantaneously with ethylene carbonate liberating CO_2 to give product *N*-phenyl ethanolamine. This reaction was found to be occurring in the pores of the catalyst and not on the surface, which was confirmed by using 4A catalyst, which has only surface Lewis acidity and pore size which is smaller than size of aniline molecule.

Conclusion of Part I and Part II indicate two different types of surface reactions (reaction mechanisms) that lead to amino alcohol formation. This may be due to the fact that the reaction conditions employed in Part I and II are completely different. In Part I, liquid phase reaction occurs between aniline and ethylene carbonate in presence of triglyme as solvent using Na-Y catalyst, while in Part II, pure aniline and ethylene carbonate react in vapor phase with Na-Y catalyst.

Therefore, systems examined in Part I and Part II can not be compared and it is difficult to arrive at a common conclusion. More work needs to be done in liquid as well as vapor phase conditions to understand the interaction of aniline and ethylene carbonate in presence of polar solvent such as triglyme with Na-Y catalyst to arrive at a definitive conclusion.

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PUBLICATIONS AND SYMPOSIA

LIST OF PUBLICATIONS

1. Carbamate synthesis by solid-base catalyzed reaction of disubstituted ureas and carbonates
   Sunil P. Gupte, Anandkumar B. Shivarkar, Raghunath V. Chaudhari
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2. Carbamate synthesis via transfunctionalization of substituted ureas and carbonates
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3. Selective synthesis of *N*,*N*-dimethyl aniline derivatives using dimethyl carbonate as methylating agent and onium salt as a catalyst
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   J. Mol. Catal. A: chem., **226**, 49 (2005).

4. Synthesis of β-amino alcohols from aromatic amines and alkylene carbonates using Na-Y Zeolite catalysts
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5. Highly active and selective Na-Y zeolite catalyzed-tandem synthesis of β-amino alcohols from aniline, dialkyl carbonate and ethylene glycol
   Anandkumar B. Shivarkar, Sunil P. Gupte, Raghunath V. Chaudhari
   Communicated

6. *N*-alkylation of aniline to β-amino alcohol using ethylene carbonate over Na-Y zeolites as a catalyst: mechanistic study by in-situ FTIR technique
   Anandkumar B. Shivarkar, Sunil P. Gupte, Shubhangi B. Umbarkar, Raghunath V. Chaudhari
   To be communicated

7. Reaction kinetic of *N*-alkylation of aniline to β-amino alcohol using ethylene carbonate in presence of Na-Y zeolite as catalyst
   Anandkumar B. Shivarkar, Sunil P. Gupte, Raghunath V. Chaudhari
   To be communicated

8. *N*,*N*-dimethylation of aromatic amines and *O*-methylation of phenols using dimethyl carbonate over immobilized ionic liquids
   Anandkumar B. Shivarkar, Lalita B. Kunde, Sunil P. Gupte, Raghunath V. Chaudhari
   To be communicated

LIST OF PATENTS

1. A process for the preparation of carbamates
   Sunil P. Gupte, Raghunath V. Chaudhari, Anandkumar B. Shivarkar, Mulla Shafeek A. Abdul
   US Patent Pub. No. *2005-0222450*
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2. Method for synthesis of β-amino alcohols
   Anandkumar B. Shivarkar, Sunil P. Gupte, Raghunath V. Chaudhari
   Filed in India, Europe, US and World, NCL-3, 2006

LIST OF SYMPOSIA PARTICIPATION

1. One pot synthesis of urethanes from addition of ureas and carbonates using solid base catalyzed reaction"
   '4th National symposium in chemistry', 1-3 February, 2002, at NCL, Pune, India.
   Poster Presentation

2. Carbamate synthesis via transfunctionalization of substituted ureas and carbonates
   '16th National Symposium and 1st Indo-German Conference on catalysis', 6-8 February, 2003, at IICT, Hyderabad, India.
   Poster Presentation (Best poster presentation award)

3. Environment friendly carboxylating agent in carbamate synthesis: Molecular structure of $[Pb_{1.5}I_5]^{-2}[(NMe_3Ph)_2]^{+2}$
   'XXXIIII National Seminar on Crystallography' 6-8 January 2004, at NCL, Pune, India.
   Poster Presentation

4. *N*-alkylation of amines by alkylene carbonates to β-amino alcohols using Na-Y and Na-X zeolite catalyst
   '17th National Symposium on Catalysis', 18-20 January 2005, at CSMCRI, Bhavnagar, India.
   Oral Presentation (Best Oral presentation award)

5. **'**6th International Symposium on Catalysis in Multiphase Reactors **(CAMURE-6)** and 5th International Symposium on Multifunctional Reactors **(ISMR-5)'**, 14-17 January 2007, at NCL, Pune, India.
   Participation

6. Highly active and selective Na-Y zeolite catalyzed-tandem synthesis of β-amino alcohols from aniline, dialkyl carbonate and ethylene glycol
   Anandkumar B. Shivarkar, Sunil P. Gupte, Raghunath V. Chaudhari
   '18th National Symposium on Catalysis', 16-18 April, 2007, at IIP, Dehradun, India.
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