DIRECT SYNTHESIS OF DIAMIDES FROM DICARBOXYLIC ACIDS AND AMINES USING Nb_2O_5 AS A BASE TOLERANT HETEROGENEOUS LEWIS ACID CATALYST

M.Sc. THESIS

A

DISSERTATION SUBMITTED IN PARTIAL

FULFILLMENT OF THE REQUIREMENT FOR THE

DEGREE OF

MASTER OF SCIENCE (M.Sc.)

IN

CHEMISTRY

SUBMITTED

BY

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SESSION: APRIL-2017

FEBRUARY, 2019

ORGANIC SYNTHESIS AND CATALYSIS LABORATORY
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THESIS ACCEPTANCE LETTER

The thesis titled **"Direct Synthesis of Diamides from Dicarboxylic Acids and Amines Using Nb_2O_5 as a Base Tolerant Heterogeneous Lewis Acid Catalyst"** submitted by Meshkatun Jannat, Roll No.: 0417032607F, Registration No.: 0417032607, Session: April-2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Master of Science (M.Sc.) in Chemistry on February 11, 2019.

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It is hereby declared that this thesis/project or any part of it has not been submitted elsewhere for the award of any degree or diploma.

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Dedicated to

My Beloved Family

&

Honorable supervisor

Acknowledgement

At the beginning, I humbly acknowledge my deepest gratitude to the Almighty, the most gracious, benevolent and merciful creator for His infinite mercy bestowed on me in carrying out the research work presented in the dissertation.

It is a great pleasure for me to acknowledge my deepest sense of gratitude, sincere, appreciation, heartfelt indebtedness and solemn regards to my reverend teacher and supervisor Dr. Md. Ayub Ali, Assistant Professor, Department of Chemistry, Bangladesh University of Engineering and Technology (BUET), for his kind supervision, indispensable guidance, valuable and constructive suggestions, liberal help and continuous encouragement during the whole period. It is obvious that his attributive contribution and efforts have greatly shaped me into what I am today. In fact, I am quite lucky to be a part of his ambitious research team.

It is my great honor to convey my sincere gratitude to my respected teacher Professor Dr. Md. Abdur Rashid, honorable Head of the Department of Chemistry, BUET for giving me his wonderful support to move through the academic processes during this M.Sc. program. I would like to convey my deepest gratitude to Professor Dr. Md. Wahab Khan for giving me an opportunity to use all instrument, apparatus from his laboratory.

I am thankful to all other respected teachers of the Department of Chemistry, BUET, for their continuous support. I would also like to thank all of the officers and staffs of the Department of Chemistry, BUET for their relentless help during my study period. My special thanks to Md. Moniruzzaman, Department of Chemistry, BUET, Dhaka for his cooperation in taking FT-IR spectrums.

I am highly thankful to Md. Jewel Hosen, scientific Officer, BCSIR, Dhaka and Md. Emdad Hossain, Scientist, WMSRC, Jahangirnagar University for characterizing of my samples.

I am grateful to Department of Glass and Ceramics Engineering, Bangladesh University of Engineering and Technology for the catalyst characterizations of XRD during my research.

I am highly grateful to all members of the board of examiners for their valuable suggestions and appreciated comments.

I am thankful to my dear consociate and all the members of Organic Synthesis and Catalysis Laboratory for their friendly cooperation and lovely encouragement throughout my research period. My special thanks to Md. Midul Islam, Asuthous Nath, Md. Olliullah, M.M.A. Shofi Uddin Sarker, Md. Johir Khan, Khadiza, Md. Kamruzzaman and Sanjoy and for their continuous help during the research.

Finally, I would like to express my heartfelt indebtedness and profound gratitude to my beloved father, mother and all of my family members for their continuous inspiration and immeasurable sacrifices throughout the period of my study.

February, 2019 Meshkatun Jannat

Abstract

Diamides are one of the most important compounds in chemical and pharmaceutical industries. Conventionally, diamides are prepared from dicarboxylic acids and amines or diamines via activated dicarboxylic acids and their derivatives such as dicarboxylic acid anhydrides or acylchlorides or through activation with a stoichiometric amount of a condensation agent. These methods have some limitations of low atom efficiency, separation of products from the reaction mixture and production of byproducts. Lewis acid catalyst was reported for amide bond formation from carboxylic acids with amines has additional drawbacks, such as limited substrate scope and high catalyst loading. These drawbacks may be caused by the suppression of Lewis acid sites of the catalyst by basic molecules (amines and water as byproduct), present in the reaction mixture. Recently, it was reported that Nb_2O_5 was used as water and base tolerant heterogeneous Lewis acid catalyst for amide bond formation.

By using the concepts of water and base tolerant properties of Nb_2O_5, diamides were synthesized from dicarboxylic acids and amines in presence of Nb_2O_5. Several Lewis and Brønsted acid catalysts were tested for the synthesis of *N, N*-dioctyl-butanediamide from succinic acid (1 mmol) and n-octylamine (2 mmol) at different conditions. Among these catalysts Nb_2O_5 showed highest catalytic activity to the corresponding *N, N*-dioctyl-butanediamide at 135 °C. After the completion of reaction catalyst was separated from the mixture by centrifugation. Other diamides were also synthesized using Nb_2O_5. The catalyst, Nb_2O_5 was reused for four cycles without a marked decrease in the yield of the product. The products were purified by recrystallization separation technique. The synthesized pure diamide products were identified by UV-VIS Spectrophotometer, FT-IR, ^{1}H-NMR and ^{13}C-NMR. Catalyst was characterized by several chemical reactions and XRD.

In conclusion, a novel, versatile and sustainable method was developed for the synthesis of diamides from dicarboxylic acids and amines using Nb_2O_5 as a base tolerant heterogeneous catalyst.

Key words: Diamide, Nb_2O_5, base tolerant, water tolerant.

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List of Abbreviations

Elaborations	Abbreviations
Broad singlet	br s
Mega Hertz	MHz
Hertz	Hz
Singlet	s
Doublet	d
Triplet	t
Quartet	q
Multiplet	m
Melting point	m.p.
Ultra Violet-Visible	UV-Vis
Infrared Spectroscopy	IR
Nuclear Magnetic Resonance	NMR
Mass Spectrometry	MS
Round bottomed flask	RB
Thin Layer Chromatography	TLC
Gas Chromatography-Mass Spectrometry	GC-MS
Proton NMR	^{1}H-NMR
Carbon-13 NMR	^{13}C-NMR
Tetrahydrofuran	THF
Coupling constant	*J*
Tetramethylsilane	TMS
Deuterated chloroform	$CDCl_3$
Hexaflorophosphate Azabenzotriazole Tetrametyl Uronium	HATU
X-ray diffraction	XRD

Chapter 1

Introduction

1.1. Introduction to Amide

Amide is a functional group which consists of a C=O (carbonyl) directly bonded to a nitrogen:

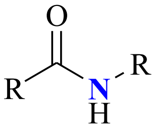


Fig. 1.1: Structure of amide

The amide functional group involves a nitrogen atom (and lone pair), but unlike an amine, the nitrogen center is not basic, due to the electron-withdrawing effect of the C=O group.

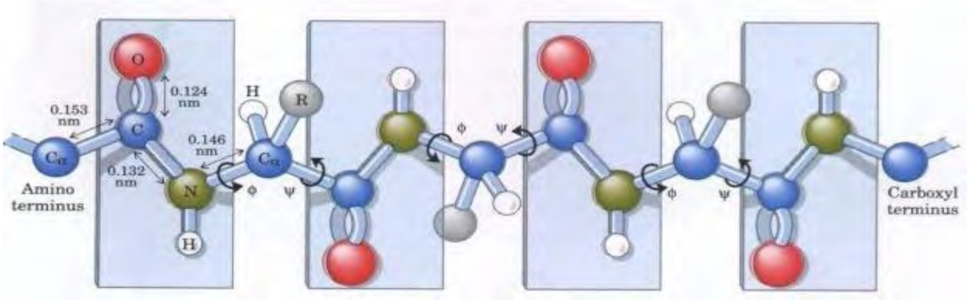
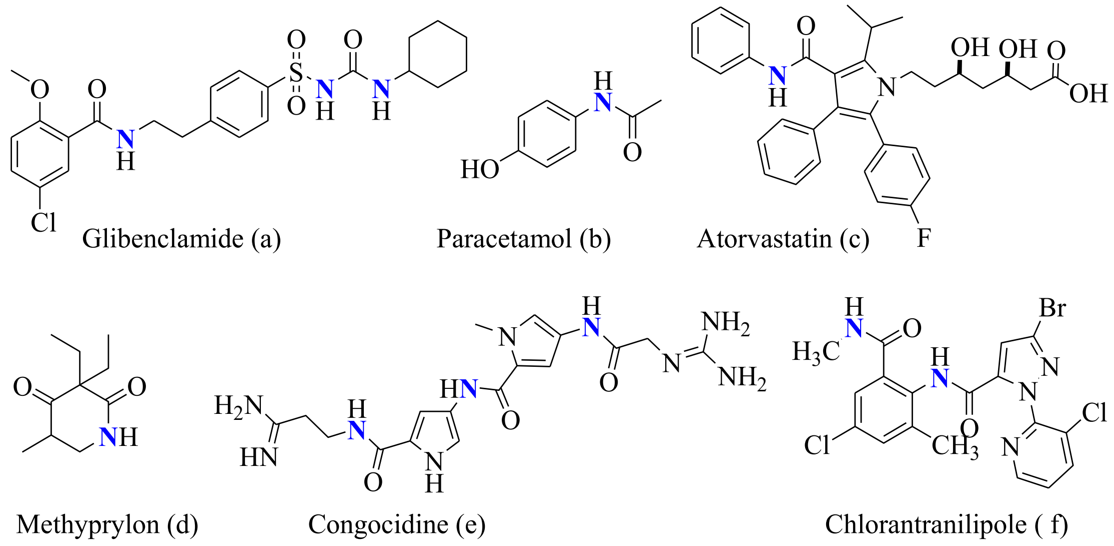


Fig. 1.1.1: Amide bond formation.

Amides functional groups are important in natural and synthetic organic compounds. It is widely present in the drugs, pharmaceuticals, natural products and agrochemicals [1]. The structural aspects of amide bonds, specifically the partial delocalization of electrons over the N-C-O bond and their hydrogen bonding abilities, play vital roles in their properties as a functional group within a larger molecule (Fig.1.1.2).



Glibenclamide (a) Paracetamol (b) Atorvastatin (c)

Methyprylon (d) Congocidine (e) Chlorantranilipole (f)

Fig. 1.1.2: Amide bonds containing drug molecules (a-d), natural products (e), pesticide (f).

1.2. Diamide

Diamide is a chemical compound containing two amide groups. In diamide two N-atoms contain two lone pairs of electrons. In diamide due to electron withdrawing effect of carbonyl oxygen nitrogen centres are not basic like amine. Diamide have same properties like amide.

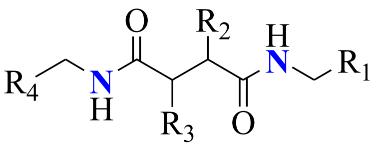
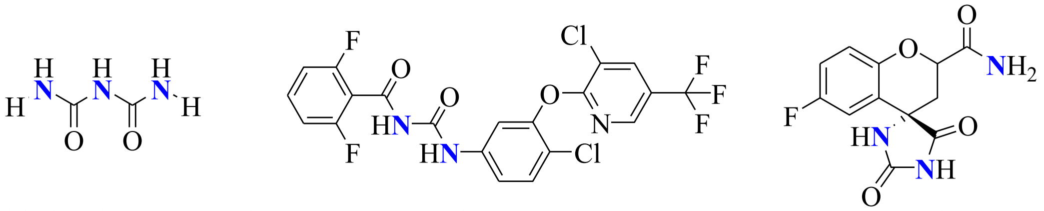


Fig. 1.2: Structure of diamide.

1.2.1. Importance of diamide

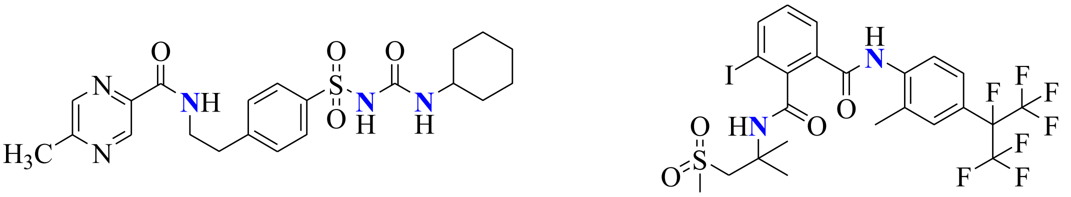
Diamide and their derivatives are an important class of compounds with numerous applications in medicinal, antiviral, pesticides, insecticides, synthetic and polymer chemistry [2-10]. Some important diamide structure is given below (Fig. 1.2.1).



Imidodicarbonic Diamide (a)

Fluazuron (b)

Fidarestat (c)



Glipizide (d)

Flubendiamide (e)

Fig. 1.2.1: Some important diamide molecules. Imidodicarbonic diamide (a), Fluazuron (b), Fidarestat (c), Glipizide (d), Flubendiamide (e).

1.3. Importance of amide bond formation reactions

Amide bond is one of the most important and studied reactions in organic chemistry. Conventional methods for amide synthesis suffer from low atom efficiency, large amount of byproducts that are unfavorable for environment profile. ACS Green Chemistry Institute and members of leading pharmaceutical corporations worldwide, identified „„amide formation avoiding poor atom economy reagents‟‟‟as one of the top challenges in organic chemistry [11]. They preferred strongly to use alternative reagents for amide bond formation avoiding the use of poor atom economy reagents received nominations and possessed in top position from all of the pharmaceutical companies in the study and have been presented as a priority area shown in Table-1:

Table -1: Priority area in amide synthesis for pharmaceutical companies.

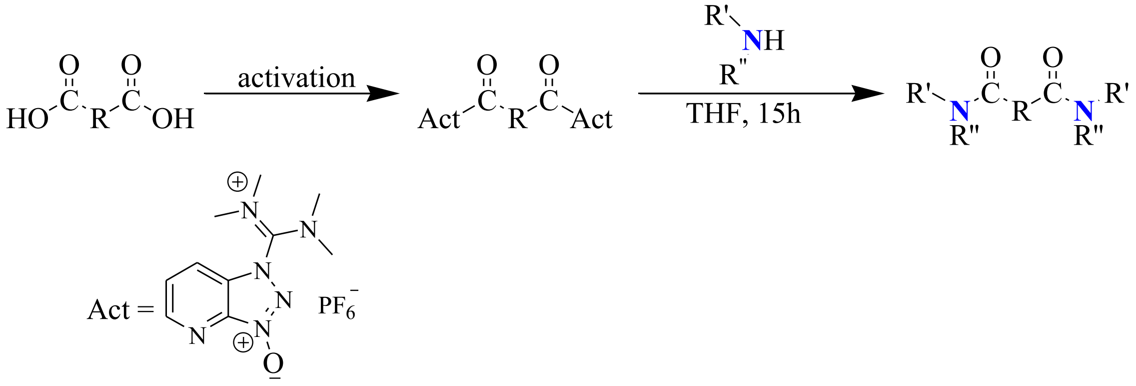
Research Area	**Number of Votes**
Amide formation avoiding poor atom economy reagents	**6**
OH activation for nucleophilic substation	5
Reduction of amides without hydride reagents	4
Safer and more environmentally friendly Mitsunobu reactions	3
Friedal-crafts reaction on an unactivated systems	2
Nitrations	2

1.4. Synthesis of diamide

1.4.1. Conventional methods

Via coupling reagent

Diamide can be synthesized by conventional method via coupling reagent. In diamide synthesis coupling reagents are used to activate carboxylic groups. It is necessary to convert -OH groups of dicarboxylic acid into a good leaving group before treatment with amine. Vimal.et.al. [12] introduced HATU to activate dicarboxylic acid groups. In this process, presence of HATU dicarboxylic acid groups converted to active ester and later addition of amine form amide bond. Due to electrophilicity, ester of dicarboxylic acid may be readily converted to acyl derivatives. These methods of amide bond formation reaction have some drawbacks to suffer from low atom efficiency and produce large amount unwanted byproducts [35].

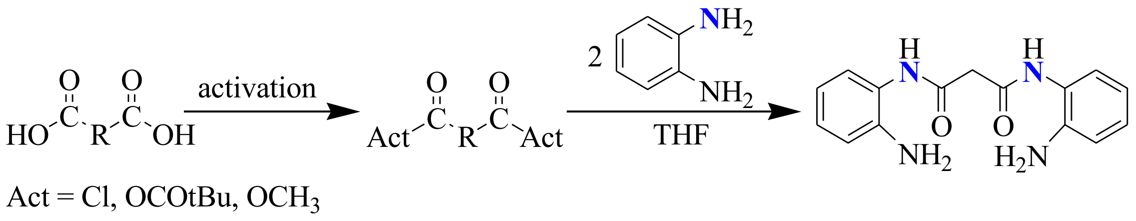


HATU (Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium)

Scheme 1.1: Principle of the activation process for amide-bond formation.

Using acylating agent

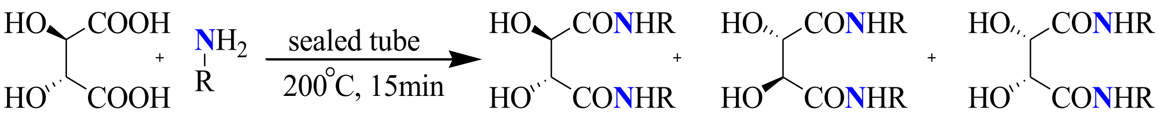
Another conventional method to synthesize diamide from dicarboxylic acids and diamines using acylating agent for activation of dicarboxylic acid [13]. This method is simple, mild and stoichiometric equivalents of acylating agent and diamine is required. Though this method is useful for diamide synthesis it has some drawbacks mixtures of diamides products and polymeric products are formed during reaction.



Scheme 1.2: Diamide synthesis via acylating agent.

Amidation of dicarboxylic acid

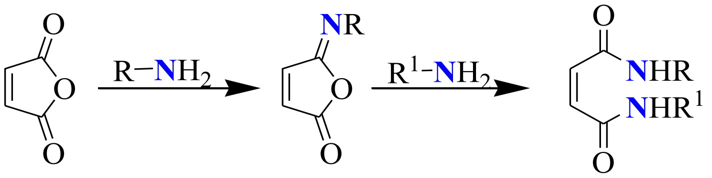
Diamide can be synyhesized from dicarboxylic acid and amines via microwave irradiation [14]. In this method, different mixtures of diamides are obtained from tartaric acid and amines. Since microwave assisted reaction certain functional can not tolerate so these method of diamide formation suffer from limited substrate scope. This method also required high temperature.



Scheme1.3: Diamide synthesis from thermolysis of *L*-tartaric acid with amines.

Amidation of anhydride

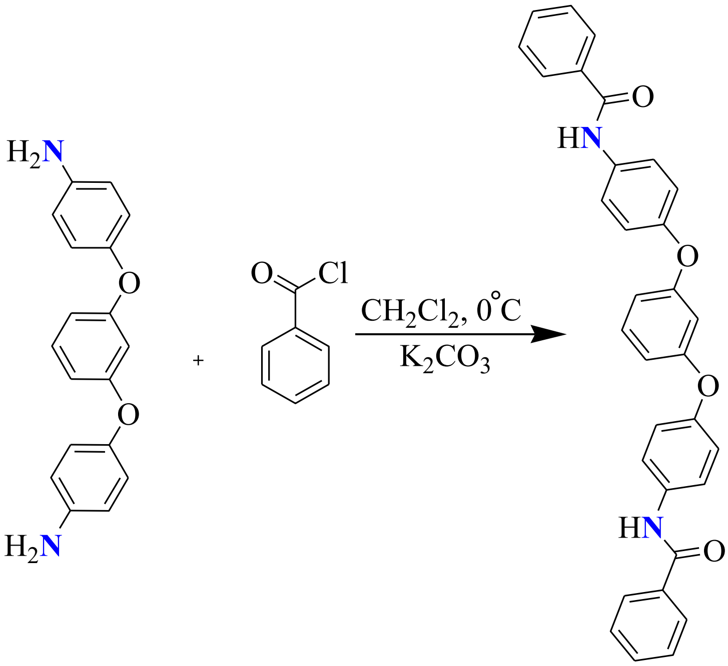
Diamide can also be synyhesized from dicarboxylic anhydride. In this method, first isoimides [15] are formed then addition of another molecule of amine formed diamides. Two types of amine are added as nucleophile. In this method, the products yield of diamide is low.



Scheme 1.4: Synthesis of diamide from carboxylic anhydride.

Amidation using diamine

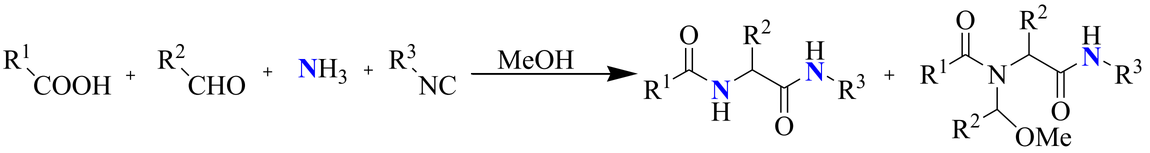
Diamides contains two amide groups are synthesized from diamine. Diamine act as electron rich, dinucleophile, easily reacts with acylhalides, aldehyde, and other groups containing electrophilic carbons or good leaving groups. Different units containing amide bonds are synthesized by reacting acyl halides and esters with diamine [20]. These methods suffer from low atom efficiency [16].



Scheme 1.5: Synthesis of diamide from acyl chloride.

Using multicomponent reaction

Ugi reaction is a four component coupling reaction important for diamide synthesis [17]. In this reaction, diamide can be synthesized from carboxylic acid, aldehyde, ammonia and nitriles via single step reaction. These methods of amide bond formations have some drawbacks large amount of byproducts produced with diamide products, suffer from low atom economy and difficulties of diamide separation from reaction mixtures.



Scheme 1.6: Diamide formation using multicomponent reaction.

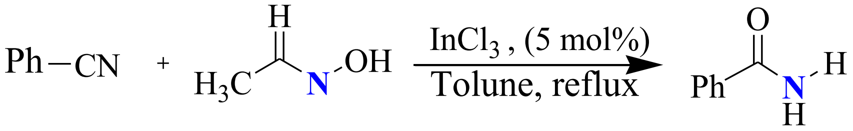
Diamide were also synthesized from tartaric acid, anthranilic acid [18, 22], steriospecific diamide was reported [19], sulphur containing diamide, N-monosubstituted terephthaladiamide, polynamide, stillbene diamide was also reported [21-26].

1.4.2. Lewis acid catalyzed amide bond formation

Since there is no reported method for the synthesis of diamide in presence of heterogeneous Lewis acid catalyst but amide bond formation using Lewis acid [30] is reported. So, we have tried to synthesis diamide using heterogeneous Lewis acid catalyst.

Homogeneous Lewis acid catalyzed amide bond formation

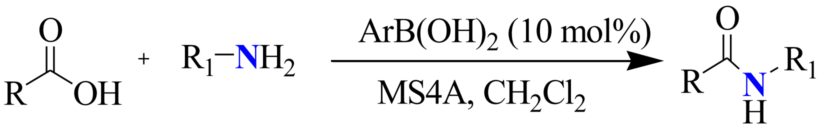
Lewis acids are important for amide bond formation. Both homogeneous and heterogeneous Lewis acids are used for amidation. Lewis acid amidation was first published [27] employed $Ti(OBu)_4$ as a catalyst for the amidation of benzoic acid with aniline. By using 2 mol% catalysts under the reflux condition of *o*-xylene, titanium butoxide complex was more effective catalyst than other Lewis acid catalyst such as $TiCl_4$, $SnCl_4$, Bu_2SnO and $BF_3.OEt_2$ [27] in the amidation of benzoic acid and aniline. In homogeneous catalytic method, amides are synthesized from carboxylic acids, esters [28], acylchloride, nitriles. Though homogeneous Lewis acid catalysts are effective for amide synthesis but it has some drawbacks reusability of catalyst and separation of product from reaction mixtures.



Scheme 1.8: In^{3+} catalyzed amide bond formation.

Lewis acid catalyzed amidation of carboxylic acid

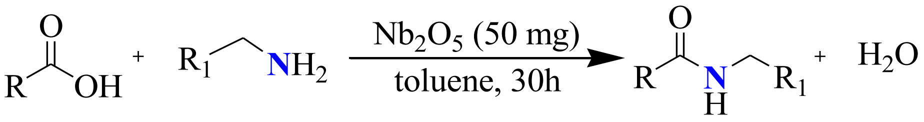
Lewis acid catalytic methods have also been developed for the amidation of carboxylic acid with amine. Boron based compounds [29-31], used in a stoichiometric fashion are effective catalysts for direct amide formation from carboxylic acid and amine. Though boron-mediated amidations are effective for amide synthesis its has some drawbacks require the removal of water from the reaction either by a dehydrating agent such as molecular sieves or by azeotropic reflux, dilute reaction conditions and an excess of either the acid or the amine is required.



Scheme 1.9: Boron based catalyzed amide bond formation.

Heterogeneous Lewis acid catalyzed amide bond formation

Using heterogeneous Lewis acid catalyst amide bond can be formed. Literature [36] showed various heterogeneous Lewis acid catalyst Nb_2O_5, TiO_2, Al_2O_3, SnO_2, ZnO, CeO_2, ZrO_2, SiO_2 were used to synthesize amide bond from carboxylic acid and amine. Among these catalysts, Nb_2O_5 was most effective for amide bond formation from carboxylic acids and amines. Due to base tolerant and water tolerant properties of Nb_2O_5 [37] showed highest catalytic activity for amide bond formation from carboxylic acid and amine.

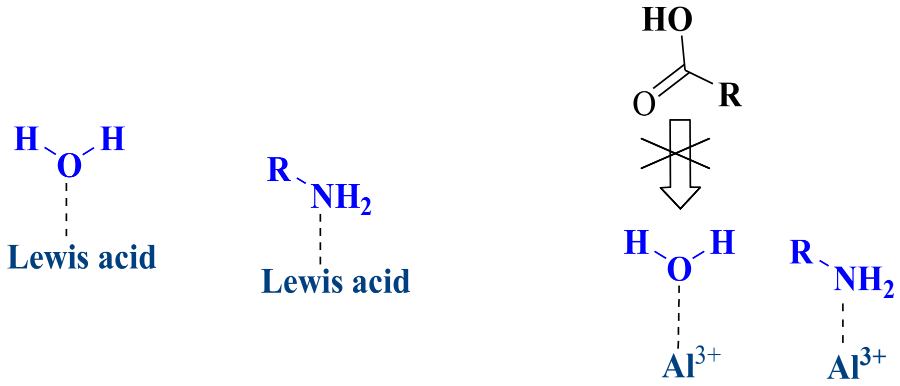


Scheme 2.1: Synthesis of amide bond using Nb^{5+} catalyst.

Amide bond also formed using triphenyl phosphine, dehydratives condensation catalysts, coupling reagent, transamidation [32-35].

1.4.3. Limitations of Lewis acid catalyzed amidation

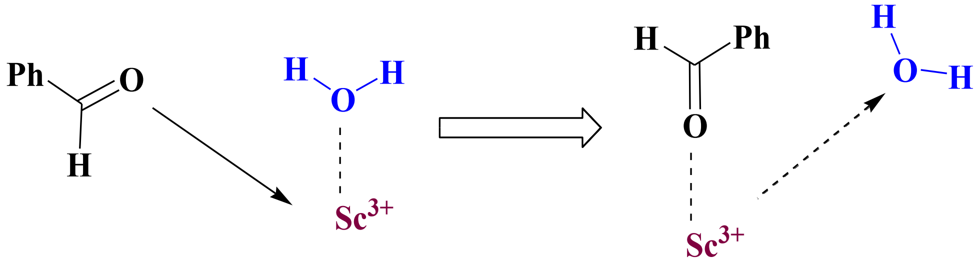
Lewis acid such as $TiCl_4$, $SiCl_4$, $AlCl_3$ can decompose [38] in the presence of small amount of water in the reaction mixture. For this reason Lewis acid catalyzed organic reactions are usually done under complete anhydrous conditions. Lewis acid catalyzed amidation reactions have additional drawbacks, such as limited substrate scope, high catalyst loading and reusability of the catalyst. In amidation reaction water produce as co-product and reaction mixtures contain amines. So, presence of basic molecules (water and amines) Lewis acidity of catalyst can be suppressed. These drawbacks can be overcome if some Lewis acid catalyst is tolerant to basic molecules (amines and water as byproduct), present in the reaction mixture for the amidation reactions.



Scheme 2.2: Water and amine suppress the Lewis acidity.

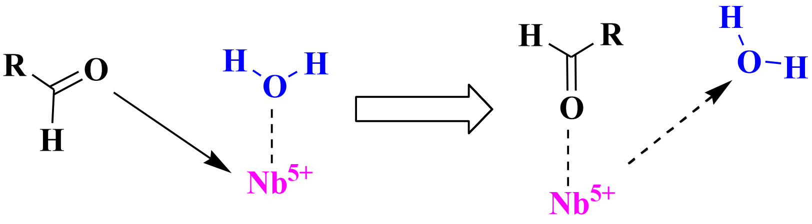
1.4.4. Water-tolerant Lewis acid catalyst

Water tolerant Lewis acid catalyst is developed. Kobayahi.et.al. showed that $Sc(OTf)_3$, $Y(OTf)_3$, $Ln(OTf)_3$ and $Yb(OTf)_3$ [39] can act as Lewis acid catalyst in water-containing solvents. They also showed that not only Sc(III), Y(III), Ln(III) but also Fe(II), Cu(II), Zn(II), Cd(II), and Pb(II) are also effective as Lewis acid catalyst in water containing solvents for the aldol reaction of benzaldehyde with silyl enol ether [39].



Scheme 2.3: Water tolerant Lewis acid catalysis of $Sc(OTf)_3$.

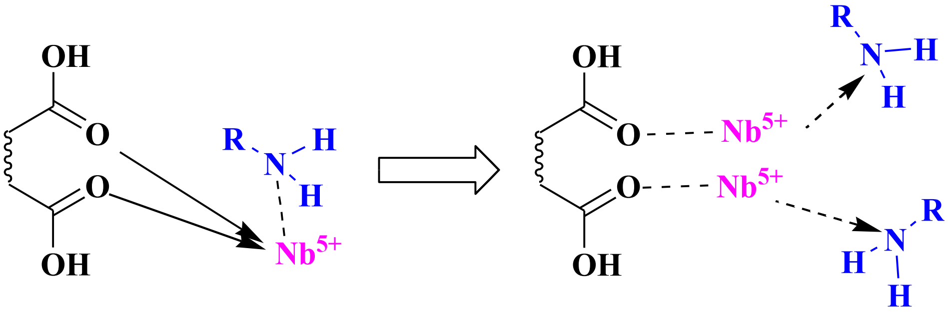
But the above catalysts are homogeneous we can not reuse these catalysts. In literature, [40] Nb_2O_5 showed as a water insoluble solid catalyst and acts as water tolerant Lewis acid catalyst. Nb_2O_5 used for amide bond formation from ester [41] and also for biofuel synthesis [42]. TiO_2 acts as supported catalyst [43].



Scheme 2.4: Water tolerant Lewis acid catalysis of Nb^{5+} [40].

1.4.5. Base-tolerant Lewis acid catalyst

Water tolerant properties of Nb_2O_5 showed in literature [40]. Recently reported [37] it was shown that Nb_2O_5 have base tolerant property used as heterogeneous Lewis acid catalyst for amide bond formation. From these concepts, we used Nb_2O_5 for synthesis of diamides from dicarboxylic acids and amines. Different Lewis, Brønsted and water-tolerant acid catalysts were examined for direct amidation of succinic acid and n-octyl amine. Among these catalysts, Nb_2O_5 showed highest catalytic activity to the corresponding *N, N*-dioctyl-butanediamide.

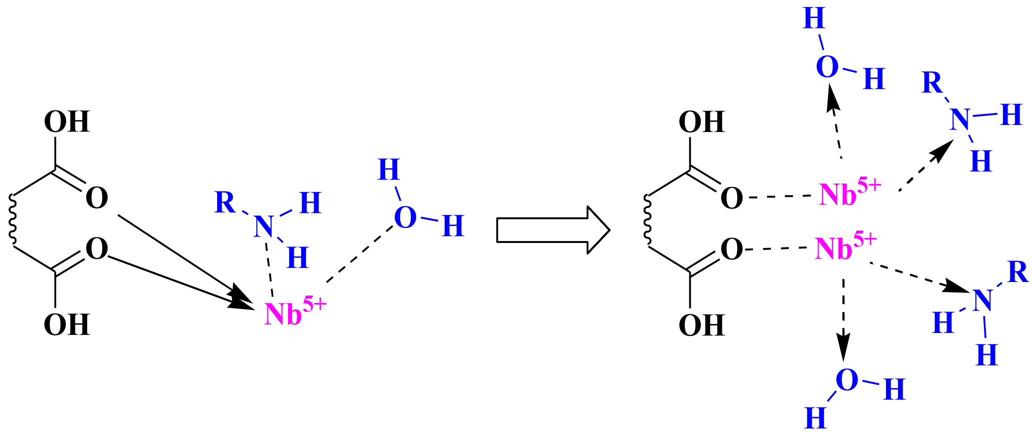


Scheme 2.5: Concept of base tolerant Lewis acid catalyzed diamide synthesis.

Since in diamide synthesis water produced as co-product and mixture containing amines. Due to water and base tolerant properties of Nb_2O_5 can tolerate both. We added water, amine and pyridine in reaction mixture using Nb_2O_5 and TiO_2 catalysts for diamide synthesis from succinic acid and n-octyl amine. Between these, Nb_2O_5 showed high catalytic activity for diamide synthesis.

1.5. Concluding remarks

To avoid the limitations of the previous method in diamides synthesis, water tolerant as well as base tolerant heterogeneous Lewis acid catalyst Nb_2O_5 can be an effective catalyst for the direct synthesis of diamides from dicarboxylic acids with amines.



Scheme 2.6: Water as well as base tolerant Nb^{5+} catalyzed diamide synthesis.

Chapter 2

Experimental

2.1. Materials and instruments

2.1.1. Chemicals and reagents

The chemicals and reagents used in this research were analytical grade and commercial grade. Ethanol, ethylacetate, aniline and benzylamine were purified by distillation. Other solvent such as acetone, n-hexane, chloroform, 2-propanol, *o*-xylene and chemicals were analytical grade used without further purification. The chemicals and reagents which were used in this research are given below:

1. Ethanol
2. Acetone
3. n-hexane
4. Toluene
5. Chloroform
5. 2-propanol
6. *o*-xylene
7. n-octylamine
8. Benzylamine
9. Succinic acid
10. Phthalic acid
11. DL-malic acid
12. Niobium pentaoxide
13. Titanium oxide
14. Aluminium oxide
15. Stannic oxide
16. Cuprous oxide
17. Sulfuric acid
18. TLC plate

2.1.2 Instruments

The research works, analysis of synthesized diamides and characterization of catalyst were done by the using following instruments:

- UV-Visible Spectrophotometer (Shimadzu-1800)
- Fourier Transform Infrared Spectrophotometer (Shimadzu FT-IR-8400)
- Nuclear Magnetic Resonance Spectrometer (Bruker BPX- 400)
- Gas Chromatography Mass Spectrometer (Shimadzu GC-MS)
- X-ray Diffractometer (Philips, Expert Pro)
- Centrifuge Machine (Model-800, China)
- Digital Balance (Precision electrical balance)
- Rotatory Evaporator
- Melting point apparatus
- Oven
- UV-light

2.2. Method of diamide synthesis

2.2.1. Calcination of catalyst

Diamide synthesis method divided into two parts first calcination of catalyst and second used of calcinated catalyst for diamide synthesis. All the purchased catalysts were stored in room temperature. For the catalyst preparation we used calcination method [44]. Commercially available Nb_2O_5 were calcined to remove water and others possible impurities. In this method, 5 g niobium pentaoxide (Nb_2O_5) was taken in a crucible kept in furnace and calcined at 500 °C for 3 h. After completing calcination Nb_2O_5 was used for diamide synthesis. Nb_2O_5 also prepared [45-49] by calcination at 400 °C, 600 °C [50]. The other catalysts such as TiO_2, Al_2O_3, SnO_2, Cu_2O were also prepared in same method by calcination at 500 °C for 3 h.

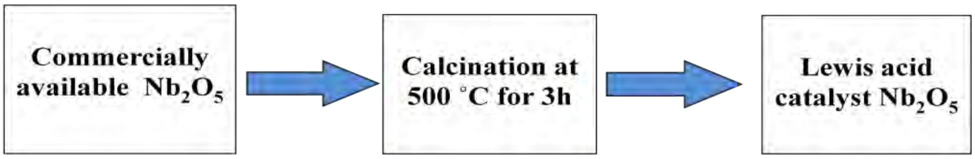


Fig. 2.2.1: Calcination of Nb_2O_5.

Calcinated catalysts

2.2.2. Diamide synthesis

In this work, diamides were synthesized via condensation reaction with dicarboxylic acids and amines in presence of heterogeneous Lewis acid catalyst. Calcinated heterogeneous Lewis acid catalysts were used as catalyst. Typically, dicarboxylic acid and amine in 1:2 ratio, 4 mL *o*-xylene and 50 mg of Nb_2O_5 were added to a reaction vessel (RB flask). The reaction mixtures was heated on hot plate at 135 °C in a sand bath and stirred at 300 rpm. After completion of the reaction, 2-propanol (4 mL) was added to the mixture, and the Nb_2O_5 catalyst was separated from reaction mixtures by centrifugation.

Again, catalytic activity was checked by model reactions (Table-2). For the model reaction, Succinic acid and n-octylamine in 1:2 ratios were added to a RB flask with 50 mg calcinated heterogeneous Lewis acid catalyst and 4 mL *o*-xylene was added to the reaction mixtures. This reaction mixture was heated on hot plate around at 135 °C in a sand bath for 30 h with continuous stirring at 300 rpm. The progress of the reaction was monitored by TLC with n-hexane (2 mL) and chloroform (1 mL). Completion of the reaction was confirmed by TLC. After the completion of the reaction, catalyst was separated from the mixture by centrifugation. The products were purified by recrystallization separation technique. The pure diamide products were confirmed by TLC and were checked by 5% $NaHCO_3$. The synthesized pure diamide products were identified by UV-VIS Spectrophotometer, FT-IR, ^{1}H-NMR, ^{13}C-NMR, GC-MS and catalyst was characterized by XRD.

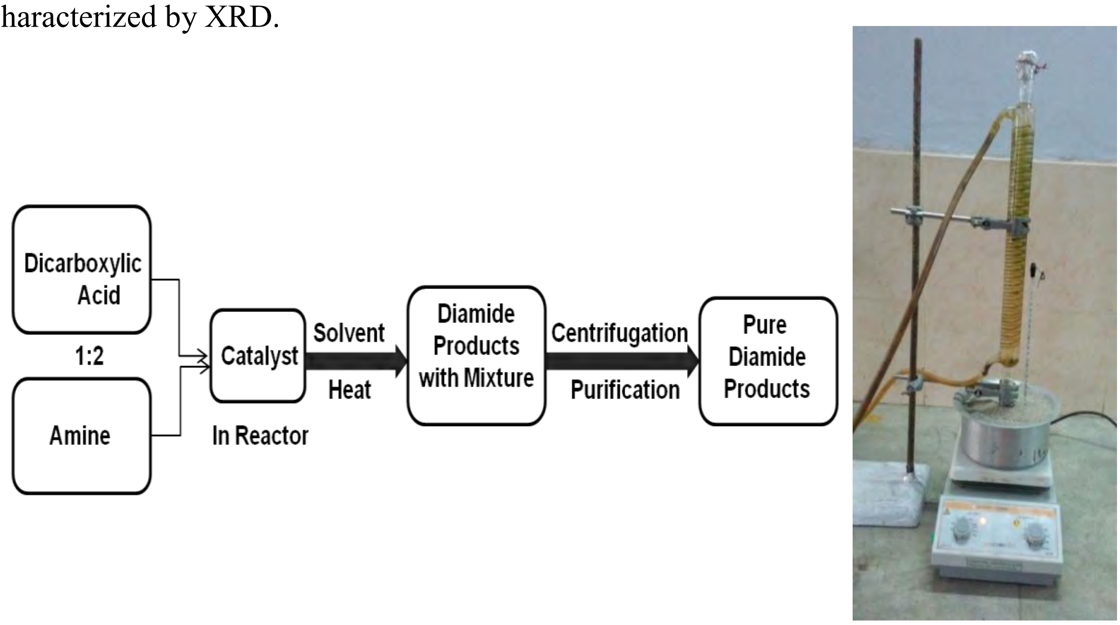
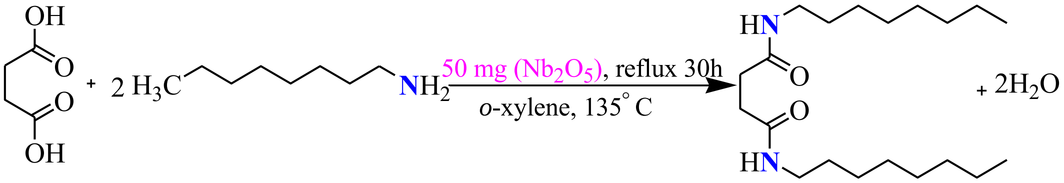


Fig. 2.2.2: Diamide synthesis using heterogeneous Lewis acid catalyst.

Synthesis of *N, N*-dioctyl-butanediamide

For synthesis of *N, N*-dioctyl-butanediamide, succinic acid (0.118g, 1 mmol) and n-octylamine (0.33mL, 2 mmol) were taken in a RB flask containing 50 mg Nb_2O_5 and then added 4 mL *o*-xylene in the mixture. This reaction mixture was heated on hot plate around at 135 °C for 30 h in a sand bath with continuous stirring of magnetic bar at 300 rpm. The progress of the reaction was monitored by TLC with n-hexane (2 mL) and chloroform (1 mL). Completion of the reaction was confirmed by TLC. After the completion of the reaction, 2 ml 2-propanol was added to dissolve diamides mixture. Then, Nb_2O_5 was separated from the mixture by centrifugation followed by washing with acetone and dried at 90°C for 3 h. The recovered Nb_2O_5 was reused for four cycles without a marked decrease in the yield of the product. The solvent was removed from mixture by rotatory evaporator. Finally, the diamide was purified by recrystallization separation technique with ethanol. For catalyst screening, solvent screening and temperature screening same reaction procedure were performed.

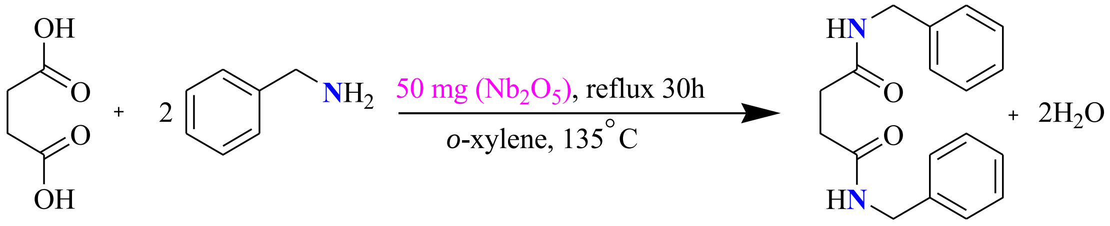


Scheme 2.7: Synthesis of *N, N*-dioctyl-butanediamide.

- Molecular weight : 340 g/mol
- Molecular formula : $C_{20}N_2O_2H_{40}$
- Melting point : 171-174 °C
- UV (λ_{max} $CHCl_3$) : 340 nm
- FT-IR (υ KBr) : 3304, 3091, 2922, 2852, 1633, 1546, 1426, 1349, 1220, 1160 cm^{-1}
- ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 6.20 (br s, 2H, -NH), 3.27-3.22 (m, 4H), 2.57 (s, 4H), 1.67 (m, 4H), 1.51-1.49 (m, 4H), 1.29-1.28 (m, 16H), 0.91-0.88 (t, *J*=6.40 Hz, 6H)
- ^{13}C-NMR (100 MHz, $CDCl_3$) : δ 172 (2C, C=O), 39.75 (2C), 31.98-31.81 (2C, C-N), 29.52-29.21 (2C), 26.92 (2C), 22.65 (8C), 14 (2C)
- GC-MS ($CDCl_3$) : m/e 340, 297, 242, 212, 156, 100

Synthesis of *N, N*-dibenzyl-butanediamide

To synthesis *N, N*-benzyl-butanediamide, succinic acid (0.118g, 1 mmol) and benzylamine (0.22 mL, 2 mmol) were taken in a RB flask containing 50 mg Nb_2O_5 and then added 4 mL *o*-xylene in the mixture. This reaction mixture was heated on hot plate around at 135 °C in sand bath for 30 h with continuous stirring of magnetic bar at 300 rpm. The progress of the reaction was monitored by TLC with n-hexane (2 mL) and chloroform (2.5 mL). Finally, completion of the reaction was confirmed by TLC. After the completion of the reaction, 2 ml 2-propanol was added to dissolve diamides mixture. Then, Nb_2O_5 was separated from the mixture by centrifugation followed by washing with acetone and dried at 90 °C for 3 h. The solvent was removed from mixture by rotatory evaporator. The diamide was purified by recrystallization separation technique with ethanol.

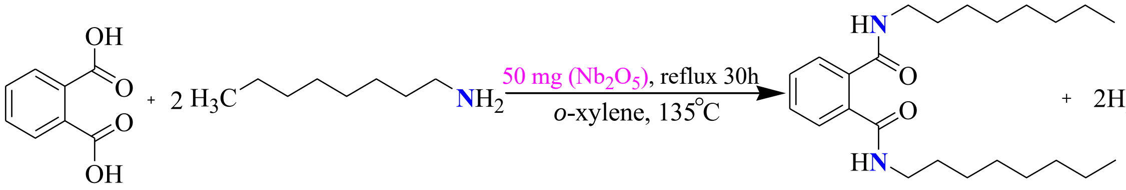


Scheme 2.8: Synthesis *N, N*-dibenzyl-butanediamide.

- Molecular weight : 296 g/mol
- Molecular formula : $C_{18}N_2O_2H_{20}$
- Melting point : 212-215 °C
- UV (λ_{max} $CHCl_3$) : 340, 258 nm
- FT-IR (υ KBr) : 3298, 3086, 2923, 1635, 1555, 1455, 1338, 1218, 1029 cm^{-1}
- ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 7.35-7.28 (m, Ar, 10H), 6.20 (br s, 2H, -NH) 4.46 (s, 4H), 2.63 (s, 4H)
- ^{13}C-NMR (100 MHz, $CDCl_3$) : δ 165 (2C, C=O), 128.72 (6C, Ar), 127.72 (4C, Ar), 127.52 (2C, Ar), 43.72 (2C), 41.50 (2C)

Synthesis of *N, N*-dioctyl-phthalamide

To synthesis *N, N*-dioctyl-phthalamide, phthalic acid (0.166g, 1 mmol) and n-octylamine (0.33 mL, 2 mmol) were taken in a RB flask containing 50 mg Nb_2O_5 and then added 4 mL *o*-xylene in the mixture. This reaction mixture was heated on hot plate around at 135 °C for 30 h in a sand bath with continuous stirring of magnetic bar at 300 rpm. The progress of the reaction was monitored by TLC with n-hexane (0.5 mL) and chloroform (2 mL). Completion of the reaction was confirmed by TLC. After the completion of the reaction, 2 ml 2-propanol was added to dissolve diamides mixture. Then, Nb_2O_5 was separated from the mixture by centrifugation followed by washing with acetone and dried at 90 °C for 3 h. The solvent was removed from mixture by rotatory evaporator. The diamide was purified by recrystallisation separation technique with ethanol and water mixture.

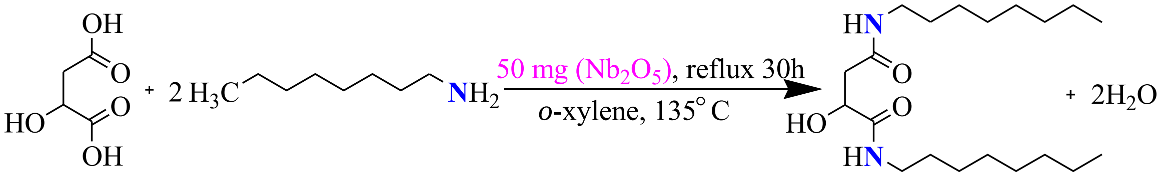


Scheme 2.9: Synthesis of *N, N*-dioctyl-phthalamide.

- Molecular weight : 388 g/mol
- Molecular formula : $C_{24}N_2O_2H_{40}$
- Melting point : 127-130 °C
- UV (λ_{max} $CHCl_3$) : 242 nm
- FT-IR (υ, KBr) : 3238, 3078, 2929, 2856, 1627, 1544, 1457, 1426, 1317, 1155, 1166 cm^{-1}
- ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 7.60-7.58, 7.47-7.45 (m, Ar, 4H), 6.78 (br s, 2H, -NH), 3.41-3.36 (m, 4H), 1.78 (m, 4H), 1.62-1.55 (m, 4H), 1.34-1.29 (m, 16H), 0.91-0.86 (t, *J*=6.40 Hz, 6H)

Synthesis of *N, N*-dioctyl-2-hydroxy-butanediamide

To synthesis *N, N*-dioctyl-2-hydroxy-butanediamide, DL-malic acid (0.135g, 1 mmol) and octylamine (0.33 mL, 2 mmol) were taken in a RB flask containing 50 mg Nb_2O_5 and then added 4 mL *o*-xylene in the mixture. This reaction mixture was heated on hot plate around at 135 °C in a sand bath for 30 h with continuous stirring of magnetic bar at 300 rpm. The progress of the reaction was monitored by TLC with n-hexane (2 mL) and chloroform (0.5 mL). Completion of the reaction was confirmed by TLC. After the completion of the reaction, 2 ml 2-propanol was added to dissolve diamides mixture. Then, Nb_2O_5 was separated from the mixture by centrifugation followed by washing with acetone and dried at 90 °C for 3 h. The solvent was removed from mixture by rotatory evaporator. The diamide was purified by recrystallisation separation technique with ethanol.

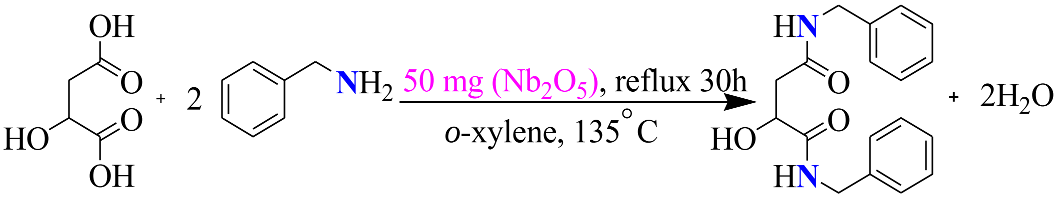


Scheme 3.1: Synthesis of *N, N*-dioctyl-2-hydroxy-butanediamide.

- Molecular weight : 356 g/mol
- Molecular formula : $C_{20}N_2O_3H_{40}$
- Melting point : 150-152 °C
- UV (λ_{max} $CHCl_3$) : 383 nm
- FT-IR (υ KBr) : 3295, 3102, 2921, 2852, 1645, 1567, 1436, 1334, 1287, 1189 cm^{-1}
- ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 7.06 (br s, 1H, -NH), 6.37 (br s, 1H, -NH), 4.38-4.36 (m, 1H, -OH), 3.29-3.22 (m, 4H), 2.80-2.76 (m, 1H), 2.66-2.60 (m, 2H), 1.53-1.49 (m, 4H), 1.29-1,28 (m, 20H), 0.91-0.88 (t, *J*=6.40 Hz, 6H)

Synthesis of *N, N*-dibenzyl-2-hydroxy-butanediamide

To synthesis *N, N*-dibenzyl-2-hydroxy-butanediamide, DL-malic acid (0.135g, 1 mmol) and benzylamine (0.22 mL, 2 mmol) were taken in a RB flask containing 50 mg Nb_2O_5 and then added 4 mL *o*-xylene in the mixture. This reaction mixture was heated on hot plate around at 135 °C in a sand bath for 30 h with continuous stirring of magnetic bar at 300 rpm. The progress of the reaction was monitored by TLC with n-hexane (2 mL) and chloroform (1 mL). Completion of the reaction was confirmed by TLC. After the completion of the reaction, 2 ml 2-propanol was added to dissolve diamides mixture. Then, Nb_2O_5 was separated from the mixture by centrifugation followed by washing with acetone and dried at 90 °C for 3 h. The solvent was removed from mixture by rotatory evaporator. The diamide was purified by recrystallization separation technique with ethanol and water mixture.



Scheme 3.2: Synthesis of *N, N*-dibenzyl-2-hydroxy-butanediamide.

- Molecular weight : 312 g/mol
- Molecular formula : $C_{18}N_2O_3H_{20}$
- Melting point : 146-150 °C
- UV (λ_{max} $CHCl_3$) : 253 nm
- FT-IR (υ KBr) : 3338, 3037, 2929, 1649, 1543, 1459, 1426, 1284, 1085 cm^{-1}
- ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 7.39-7.25 (m, Ar, 10H), 6.74 (br s, 2H, -NH) 4.43-4.42 (m, 4H), 2.89-2.84 (m, 1H), 2.72-2.66 (m, 2H), 1.93 (m, -OH, 1H)

2.3. Characterization of synthesized product

2.3.1. UV-visible spectrophotometer

The UV-Visible spectral analysis was performed with a double beam UV-Visible spectrophotometer. The analyses were involved within 200-800 nm range [58, 59]. For, UV-Vis spectral analyses, purified and dried diamides were dissolved in chloroform solvent. The dissolved sample was placed in the sample cuvette while the reference cuvette was filled with the corresponding solvents. All the analyses were performed at room temperature 30°C (±2°C).

2.3.2. Fourier transform infrared (FTIR) analysis

The infrared spectra of the synthesized diamides were recorded on an FT-IR spectrometer in the region of 4000-500 cm^{-1}. All the 5 diamide samples had dried. A small portion of samples were taken and mixed with KBr [58, 59]. The powder mixtures were then compressed in a metal holder under pressure to make pellets. The pellets were then placed in the path of IR beam for measurements.

2.3.3. Nuclear magnetic resonance (NMR) analysis

^{1}H and ^{13}C-NMR spectra were recorded by Bruker BPX- 400 spectrometer operating at 400 MHz and 100 MHz respectively and $CDCl_3$ used as solvent, tetramethylsilane (TMS) as an internal standard. All chemical shifts (δ) were reported in ppm and coupling constants (J) in Hz. Chemical shifts were performed relative to tetramethylsilane (TMS) and *d*-solvent peaks (7.28 ppm in ^{1}H and 77.00 ppm in ^{13}C, chloroform), respectively. Abbreviations used in the NMR experiments: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet [58, 59].

2.3.4. Gas chromatography mass spectrum (GC-MS) analysis

Retention time and mass spectrum for *N, N*-dioctyl-butanediamide was recorded using column: Rxi-5ms, 30m, 0.25mm ID, 0.25µ df by Shimadzu GC-MS. To determine mass spectrum the molecule bombarded with high electron beam then form molecular ion again fragmentation of molecular ion occurs form many fragment ions.

2.3.5. X-ray diffraction (XRD)

X-ray diffraction (XRD) pattern were performed for calcinated niobium pentaoxide at 500 °C before used in reaction and after four cycles in the powder state. The powder samples were pressed in a square aluminum sample holder (40 mm × 40 mm) with a 1 mm deep rectangular hole (20 mm x 15 mm) and pressed against an optical smooth glass plate. The upper surface of the sample was labeled in the plane with its sample holder. The sample holder was then placed in the diffractometer.

2.3.6. Melting Point

Melting points of diamides were determined in open capillary tubes in melting point apparatus.

2.3.7. Solubility

All the diamides were soluble in chloroform.

Chapter 3

Results and Discussions

3.1. Catalyst Screening

Screening catalysts, involving heterogeneous and Brønsted acid catalysts, for a model reaction of 1 mmol of succinic acid with 2 mmol of n-octylamine at 135 °C under reflux conditions for 30 h. Table-2, Fig. 3.1 summarizes the yield of the corresponding diamide for various heterogeneous and Brønsted acid catalyst. Under the conditions, the thermal reaction in the absence of catalyst gave only 1% yields of the diamide (entry-1). We screened 7 types of metal oxides (entries 2-6) and Brønsted acid catalyst (entry-7). Among these catalysts, Nb_2O_5 shows the highest yield (95%) for the corresponding diamide.

Diamide formation reaction is a condensation reaction; water produced during the reaction can suppress the catalytic activity by strong adsorption on acid sites of catalysts. Thus, water tolerant acid catalysts may be effective for the reaction.
In presence of Brønsted acids such as sulfuric acid (entry-7) no diamide product was obtained.

3.2. Solvent screening

In solvent screening, three solvent were used for the model reaction. Among these, *o*-xylene is preferable solvent for the diamide synthesis. We also observe without solvent reaction does not occurred. Table-3, Fig. 3.2 shows the result of solvent screening.

3.3. Effect of amine for model reaction

The effect of amines was analyzed for model reaction on Nb_2O_5 and TiO_2 catalyst in Table-4, Fig. 3.3. The model reaction was performed for different ratios of succinic acid and n-octylamine among these 1:2 shows the highest catalytic activity for Nb_2O_5. We also observed when increasing the ratio of n-octylamine the percentage of yield decreased this is happened because Lewis acid interact with n-octylamine instead of succinic acid. The interaction is lower in case of Nb_2O_5 than TiO_2. So, it is said that Nb_2O_5 is higher tolerant to basic amine present in reaction mixture than TiO_2.

3.4. Effect of calcinations temperature of Nb_2O_5 for model reaction

The effect of calcinations temperature is shown in Table-5, Fig. 3.4. Nb_2O_5 was calcined at 400°C, 500°C and 600°C [50] for 3h. After calcinations, Nb_2O_5 was used for model reaction. From these calcinated Nb_2O_5, 500°C calcinated Nb_2O_5 show the highest catalytic activity for diamide synthesis. In literature showed at 500°C calcinated Nb_2O_5 contains larger number of active Nb^{5+} sites [51] on its surface and surface area is higher in these temperature. Nb_2O_5 shows high surface acidity [56] and used for for cyclization of dicarboxylic acids to cyclic anhydrides as monomers for bioplastics [57].

3.5. Lewis acidity of Nb_2O_5

Literature, [36] showed Nb_2O_5 was used for activation of C=O bond of carboxylic acid. The surface area of 500°C calcinated Nb_2O_5 54 m^2g^{-1} and turn over number 341 [36] with respect to Lewis acid site. The heterogeneous catalyst used for amide bond formation [52-55]. IR study of pyridine adsorption on Nb_2O_5, showed that surface acid sites of dehydrated Nb_2O_5 are mainly Lewis acidic sites (exposed Nb^{5+} cations). Fig. 3.5 shows the IR spectrum of pyridine adsorbed on dehydrated and rehydrated Nb_2O_5. These spectra have basically the same features; the band at 1445 cm^{-1} due to coordinated pyridine on Lewis acid site (exposed Nb^{5+} cations) is dominant rather than the band at 1540 cm^{-1} due to pyridinium ion due to Brønsted acid sites. The result shows that water does not essentially change the IR spectrum of adsorbed pyridine; Nb_2O_5 is predominantly Lewis acidic even after re-hydration. IR studies of acetic acid adsorbed on the catalysts shows strong acid-base interaction between the Nb^{5+} Lewis acid site and carbonyl oxygen of the acetic acid, which can result in high activity of Nb_2O_5. The spectrum (Fig. 3.5.1) showed a C=O stretching band of the adsorbed acetic acid ($\nu_{C=O}$) at lower wavenumber (1686 cm^{-1}) than non Lewis acidic oxide, SiO_2 (1703 cm^{-1}) and conventional Lewis acidic oxides: TiO_2 (1695 cm^{-1}) and Al_2O_3 (1697 cm^{-1}) [36]. So, from the literature concept, it is said that the surface of Nb_2O_5 is most effective Lewis acid sites for activation of the C=O bond of the dicarboxylic acid other than TiO_2 and Al_2O_3.

3.6. Base tolerant catalysis of Nb_2O_5 for amidation

We have also analyzed the effect of base (water and pyridine) on Nb_2O_5 and TiO_2 for the amidation of succinic acid and n-octylamine by adding water and pyridine in reaction system (Table-6).

To compares base tolerance property of Nb_2O_5 and TiO_2, we measured the yield of the diamide in the model reaction for 30 h with Nb_2O_5 or TiO_2 under the reflux conditions in the presence of 1 mmol and 0.5 mmol of basic additives: H_2O, pyridine. The negative effects of the additives were lower for Nb_2O_5 than TiO_2. This suggests that the active site (Nb^{5+} Lewis acid site) interacts preferentially with the reactant (dicarboxylic acid) in the presence of basic molecules. Summarizing the above results, we can conclude that Lewis acid site of Nb_2O_5 has higher tolerance to basic molecules than TiO_2 conventional solid Lewis acid.

3.7. Reusability of Nb_2O_5

We have studied the reusability of Nb_2O_5 for the model reaction after the completion of reaction catalyst was separated from the mixture by centrifugation, followed by washing with acetone, and by drying at 90 °C for 3h [36]. The recovered catalyst was reused for four times without a marked loss of its catalytic activity (Fig. 3.7).

3.8. Characterization of catalyst

X-ray diffraction (XRD) pattern shown in Fig. 3.8 of calcinated niobium pentaoxide at 500 °C before used in reaction and Fig. 3.8.1 after four cycles in the powder state. XRD data showed the phase of Nb_2O_5 does not mark change even after four cycles used in reaction. So, Nb_2O_5 acts as reusable heterogeneous Lewis acid catalyst for diamide synthesis from dicarboxylic acids and amines.

Model reaction

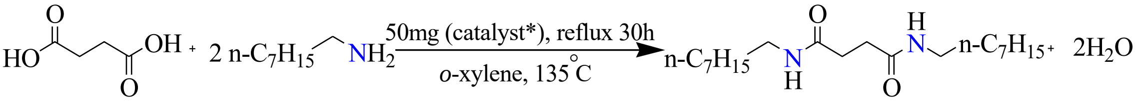


Table-2: Catalyst screening for model reaction.

Entry	Catalyst*	Yield (%)
01	no catalyst	1
02	Nb_2O_5	95
03	TiO_2	75
04	Al_2O_3	50
05	SnO_2	45
06	Cu_2O	20
07	H_2SO_4	0

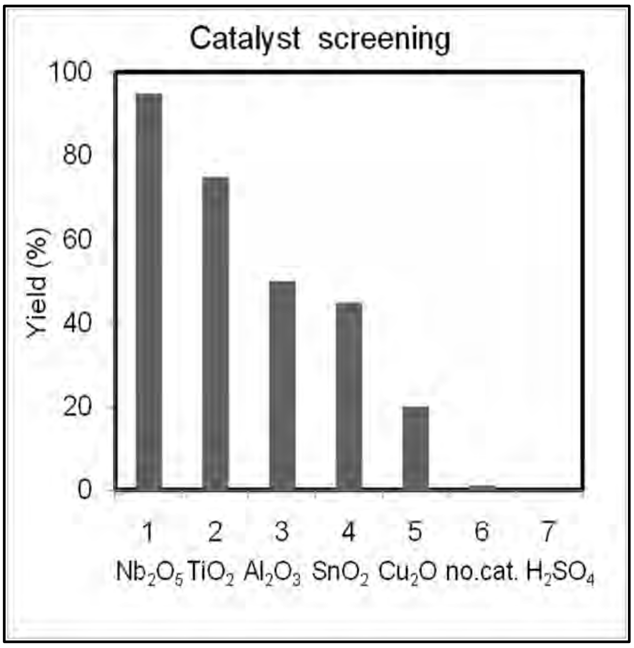


Fig. 3.1: Catalyst screening for model reaction.

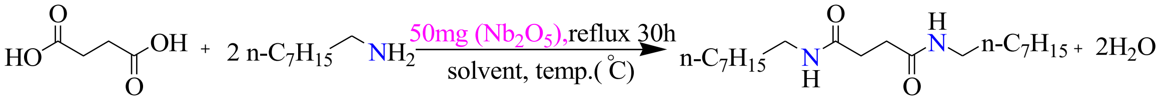


Table-3: Solvent screening for model reaction.

Entry	Solvent	Temperature (°C)	Yield (%)
01	*o*-xylene	135°C	95
02	Toluene	reflux	55
03	n-hexane	reflux	0
04	Without solvent	135°C	0

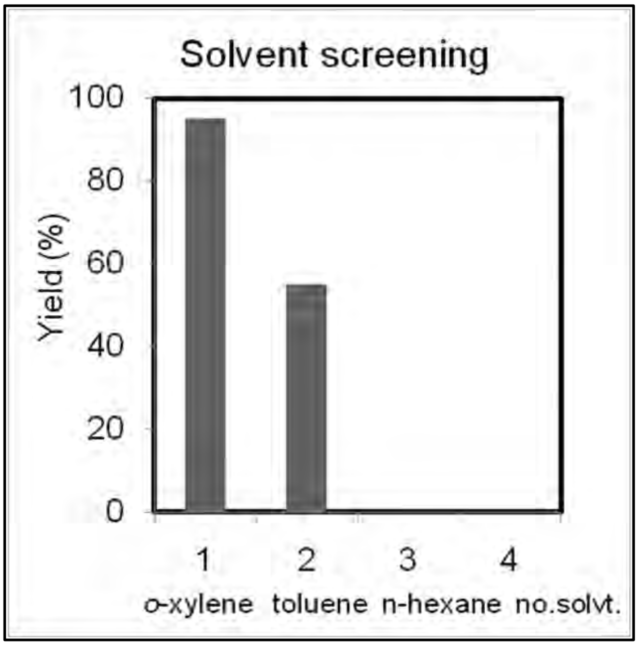


Fig. 3.2: Solvent screening for model reaction.

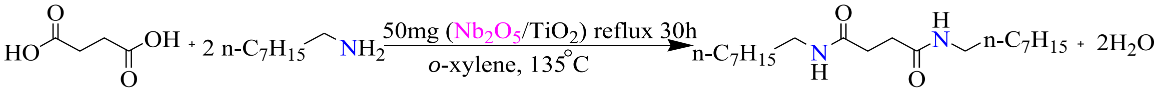


Table-4: Effect of amine for model reaction.

Entry	Reaction ratio	Yield (%) Using (Nb_2O_5)	Yield (%) Using (TiO_2)
1	1:2	95	75
2	1:3	94	72
3	1:4	91	60
4	1:5	88	45
5	2:1	No reaction	No reaction

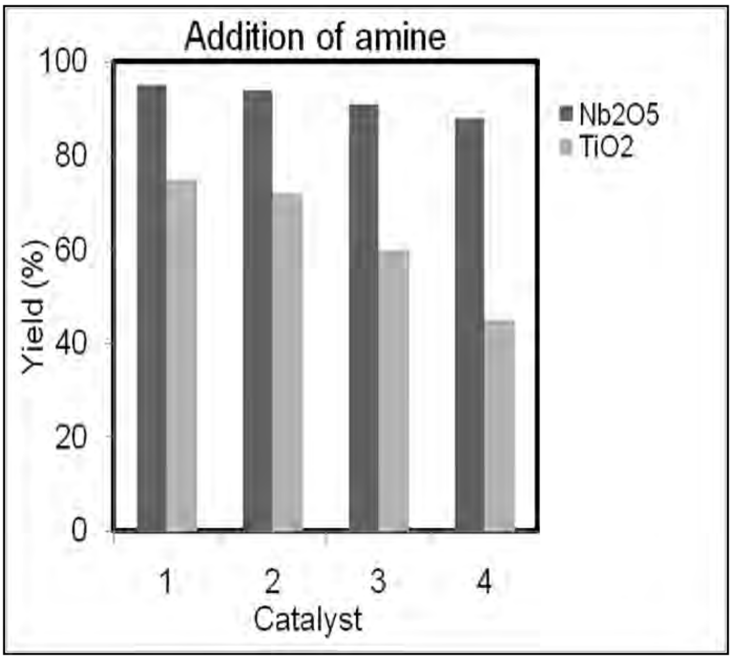


Fig.3.3: Effect of amine for model reaction.

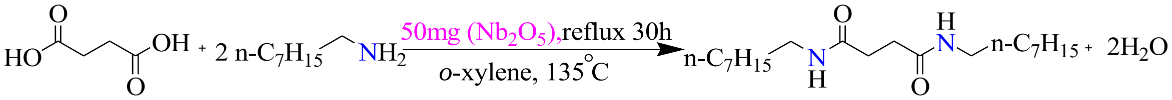


Table-5: Effect of calcination temperature of Nb_2O_5 for model reaction.

Calcination temperature (° C)	Yield (%)
400	65
500	95
600	70

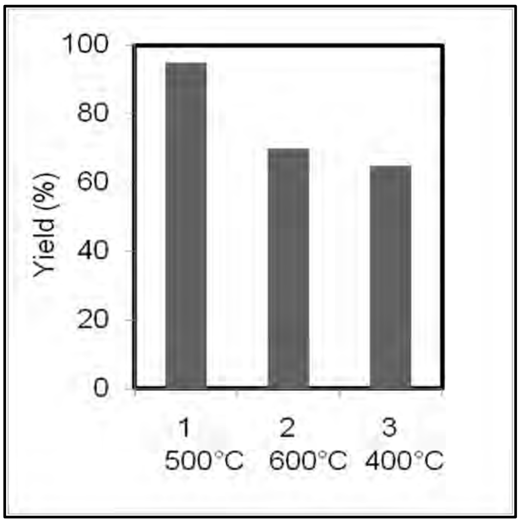


Fig. 3.4: Effect of calcination temperature for model reaction.

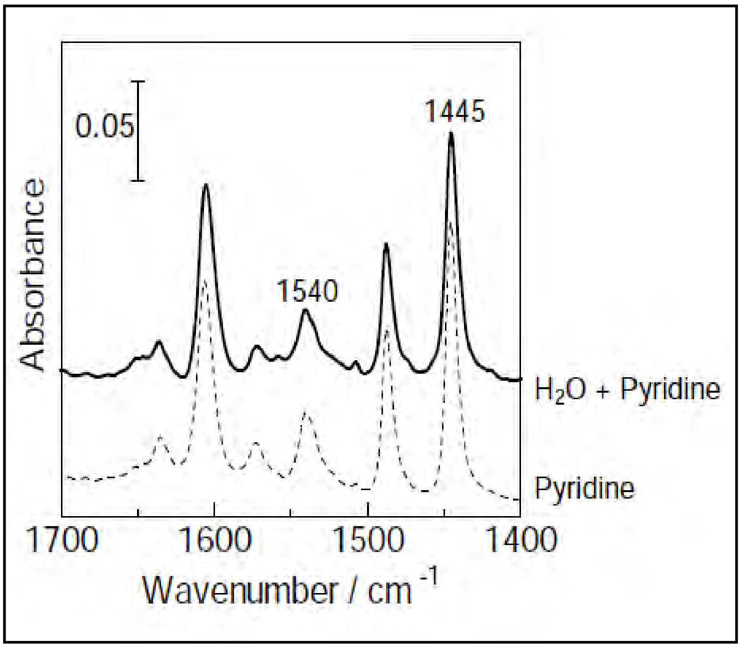
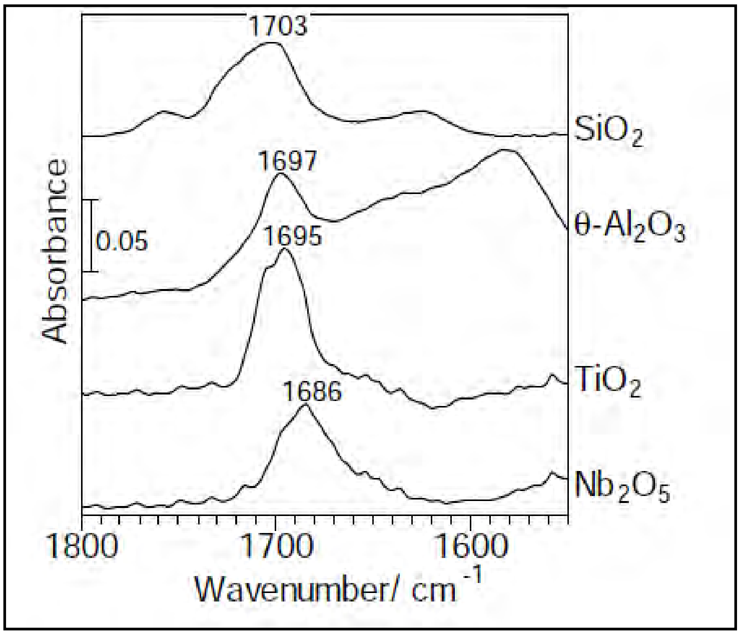


Fig. 3.5: FT-IR spectrum of adsorbed pyridine on dehydrated Nb_2O_5 (dashed line) and rehydrated Nb_2O_5 (solid line) at T=200°C [36].



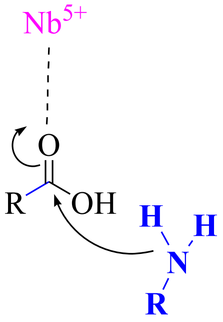


Fig. 3.5.1: FT-IR spectrum of acetic acid adsorbed on Nb_2O_5, TiO_2, ϴ-Al_2O_3 and SiO_2 at -75°C [36].

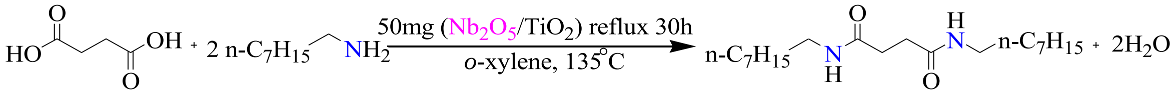


Table-6: Effect of water and pyridine for model reaction.

Entry	Water/Pyridine	Yield (%) Using (Nb_2O_5)	Yield (%) Using (TiO_2)
1	without (H_2O/Py)	95	75
2	1mmol (H_2O)	93	71
3	0.5mmol (Py)	92	64
4	1mmol (Py)	89	52

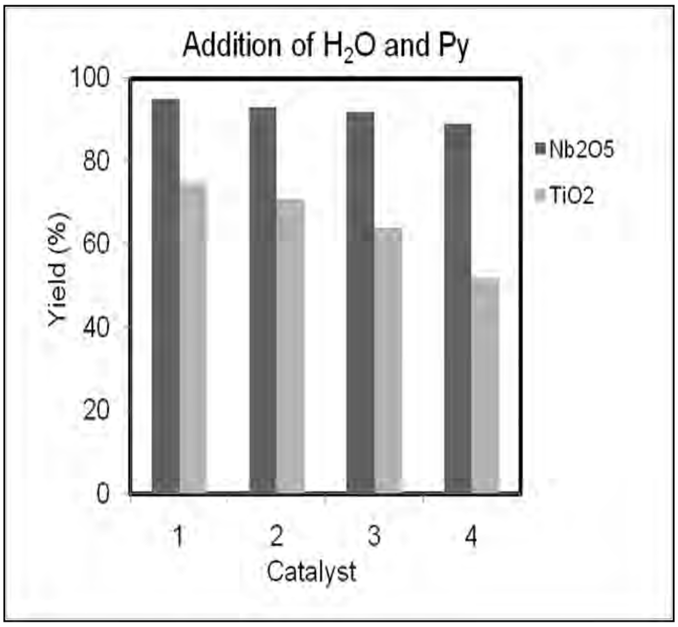
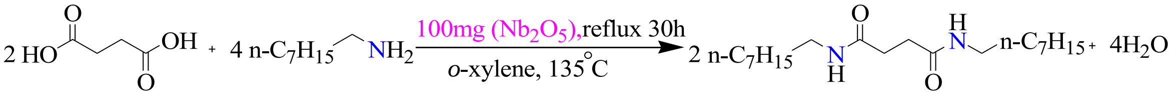


Fig. 3.6: Effect of water and pyridine for model reaction.



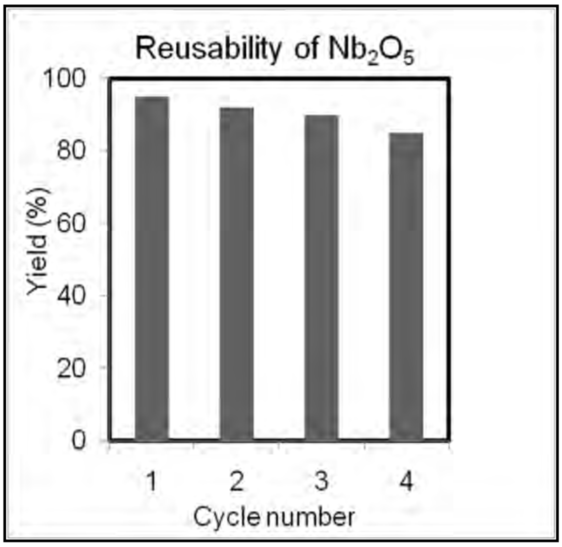


Fig. 3.7: Reusability of Nb_2O_5 (100 mg) for amidation of succinic acid and n-octylamine in *o*-xylene reflux for 30 h.

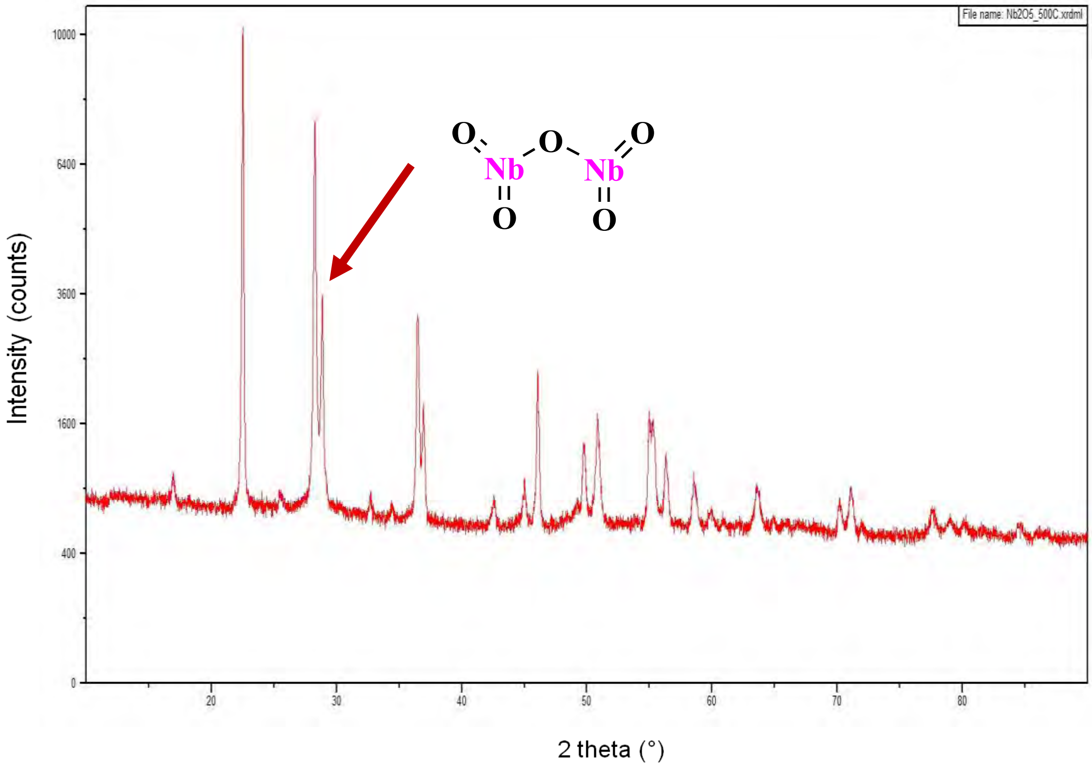


Fig. 3.8: XRD of Nb_2O_5 calcinated at 500°C before used in reaction.

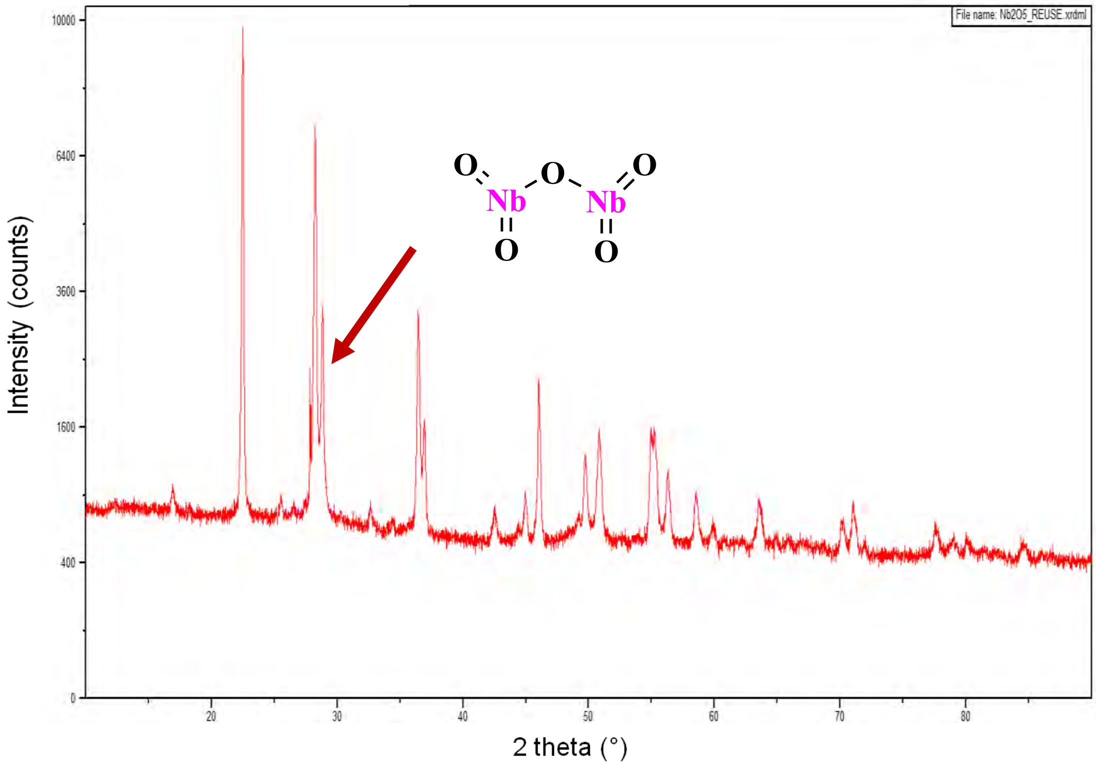
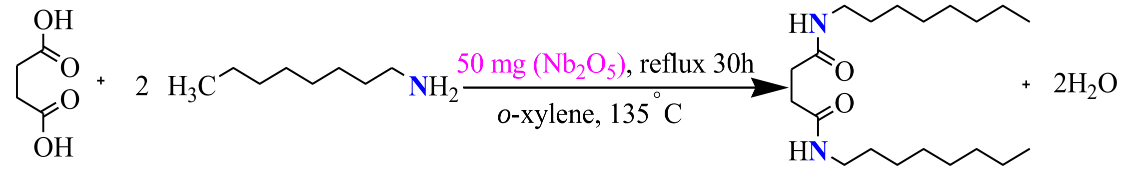


Fig. 3.8.1: XRD of Nb_2O_5 after four times used in reaction.

3.9. Characterization of Synthesized diamide

3.9.1. Characterization of Synthesized *N, N*-dioctyl-butanediamide

The diamide-1 was synthesized by refluxing 1:2 molar ratios of succinic acid (0.118g) and n-octylamine (0.33 mL) in *o*-xylene (4 mL) presence of 50 mg Nb_2O_5 heated on hot plate around at 135 °C in a sand bath for 30 h with continuous stirring of magnetic bar at 300 rpm. The progress of the reaction was monitored by TLC with n-hexane (2 mL) and chloroform (1 mL).



1

After purification diamide-1 characterized by the following way:

A white solid was obtained molecular formula $C_{20}N_2O_2H_{40}$ with 95% yield, m.p 171-174 °C. The structure of the compound was established by various spectral analyses.

i) UV-visible spectroscopy:

The UV-visible spectrum (Fig. 3.9.1(a), page no. 52) of the diamide-1 showed the following peak:

- ✓ λ_{max} 340 nm : n→π* transition of C=O and presence of –NHR auxochrome.

ii) FT-IR spectroscopy:

The FT-IR (KBr) spectrum (Fig. 3.9.1 (b), Page no. 52) of the diamide-1 exhibited a number of bands, some of which were assigned as the follows at υ cm^{-1} :

✓ 3304.17 : -NH str. of amide bond.
✓ 3091 : Overtone of –NH bending.
✓ 2922.25 : -C-H str. of -CH_3 (asy).
✓ 2852.81 : -C-H str. of –CH_2 (sym).
✓ 1633.76 : C=O str. for amide bond.
✓ 1546.96 : -NH bend.
✓ 1426.41 : -CH_2 bend.
✓ 1349.35 : -CH_3 bend.
✓ 1220 : -C-N bend.
✓ 1160.22 : -C-O bend.

iii) ^{1}H-NMR spectroscopy:

The ^{1}H-NMR spectrums (Fig. 3.9.1 (c), Page no. 53) of diamide-1 exhibited signals (in δ ppm) which were assigned as follows:

✓ 6.20 (br s, 2H, -NH)) : two protons of two amide bond at (N-9, 14).
✓ 3.27-3.22 (m, 4H) : four protons at (C-8, C-15)
✓ 2.57 (s, 4H) : four protons at (C-11, C-12)
✓ 1.67 (m, 4H) : four protons at (C-7, C-16)
✓ 1.51-1.49 (m, 4H) : four protons at (C-6, C-17)
✓ 1.29-1.28 (m, 16H) : sixteen protons at (C-2,3,4,5,18,19,20,21)
✓ 0.91-0.88 (t, *J* =6.40 Hz, 6H) : six protons at (C-1, C-22)

iv) ^{13}C-NMR spectroscopy:

The ^{13}C-NMR spectrum (Fig. 3.9.1 (e), Page no. 55) of diamide-1 showed several signals (in δ ppm) which were assigned as follows:

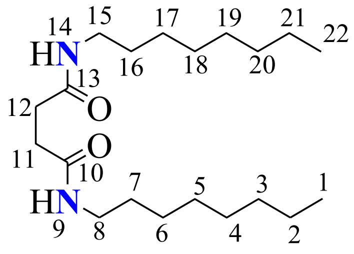
- ✓ 172 (2C, C=O) : two carbonyl carbon at (C-10, 13)
- ✓ 39.75 (2C) : two carbon at (C-11, 12)
- ✓ 31.98-31.81 (2C, C-N) : two carbon at (C-8, 15)
- ✓ 29.52-29.21 (2C) : two carbon at (C-7, 16)
- ✓ 26.92 (2C) : two carbon at (C-6, 17)
- ✓ 22.65 (8C) : eight carbon at (C:2-5, 18-21)
- ✓ 14 (2C) : two carbon at (C-1, 22)

(v) GC-MS spectrometry:

The GC-MS spectrum (Fig.3.9.1 (g), Page no. 57) of the diamide-1 exhibited retention time (in min) mass spectrum (in m/e):

- ✓ Retention time : 21.925
- ✓ Molecular ion peak (m/e) : 340
- ✓ Base peak (m/e) : 212

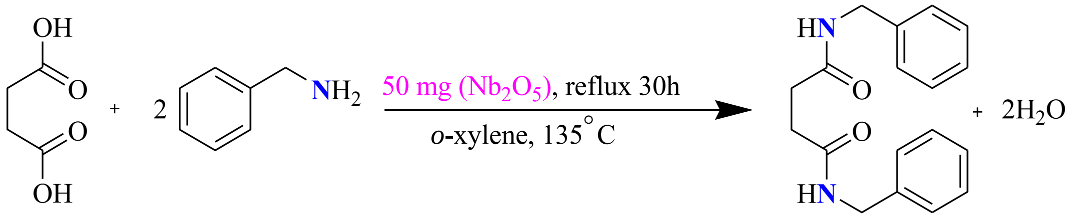
The total forty (40) proton atoms, twenty (20) carbon atoms and molecular weight 340 g/mol were obtained in the compound by ^{1}H-NMR, ^{13}C-NMR and GC-MS spectra. The spectral data of UV, FT-IR, ^{1}H-NMR, ^{13}C-NMR and GC-MS data are compatible with the structure of this compound shown as below:



1

3.9.2. Characterization of Synthesized *N, N*-benzyl-butanediamide

The diamide-2 was synthesized by refluxing 1:2 molar ratios of succinic acid (0.118g) and benylamine (0.22 mL) in *o*-xylene (4 mL) presence of 50 mg Nb_2O_5 heated on hot plate around at 135 °C for 30 h in a sand bath with continuous stirring of magnetic bar at 300 rpm. The progress of the reaction was monitored by TLC with n-hexane (2 mL) and chloroform (2.5 mL).



2

After purification diamide-2 characterized by the following way:

A white solid was obtained molecular formula $C_{18}N_2O_2H_{20}$ with 80% yield, m.p. 212-215 °C. The structure of the compound was established by various spectral analyses.

i) UV-visible spectroscopy:

The UV-visible spectrum (Fig.3.9.2 (a), Page no. 58) of the diamide-2 showed the following peak:

- ✓ λ_{max} 340.50 nm: n→π* transition of C=O and presence of –NHR auxochrome and π→π* due to C=C, 258.50 nm.

ii) FT-infrared spectroscopy:

The FT-IR (KBr) spectrum (Fig. 3.9.2 (b), Page no. 58) of the diamide-2 exhibited a number of bands, some of which were assigned as the follows at υ cm^{-1}:

- ✓ 3298.38 : -NH str. of amide bond.
- ✓ 3086.21 : = C-H str. of aromatic.
- ✓ 2923.22 : -C-H str. of –CH_2 (sym).
- ✓ 1635.69 : C=O str. for amide bond.
- ✓ 1555.64 : -NH bend.
- ✓ 1455.34 : C=C of aromatic
- ✓ 1338.64 : -CH_2 bend.
- ✓ 1218 : -C-N bend.
- ✓ 1029 : -C-O bend.

iii) ^{1}H-NMR spectroscopy:

The ^{1}H-NMR spectrums (Fig.3.9.2 (c), Page no. 59) of the diamide-2 exhibited signals (in δ ppm) which were assigned as follows:

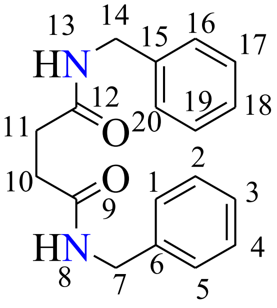
- ✓ 7.35-7.28 (m, 10H) : ten protons of two phenyl groups (C:1-5, C:16-20)
- ✓ 6.20 (br s, 2H, -NH) : two protons of two amide bond at (N-8, N-13)
- ✓ 4.46 (s, 4H) : four protons at (C-7, C-14)
- ✓ 2.63 (s, 4H) : four protons at (C-10, C-11)

iv) ^{13}C-NMR spectroscopy:

The ^{13}C-nmr spectrum (Fig.3.9.2 (e), Page no. 61) of the diamide-2 showed several signals (in δ ppm) which were assigned as follows:

- ✓ 165 (2C, C=O) : two carbonyl carbon at (C-9, 11)
- ✓ 128.72 (6C, Ar) : six aromatic carbon at (C-1, 5, 6, 15, 16, 20)
- ✓ 127.72 (4C, Ar) : four aromatic carbon at (C-2, 4, 17, 19)
- ✓ 127.52 (2C, Ar) : two aromatic carbon at (C-3, 18)
- ✓ 43.72 (2C, C-N) : two carbon at (C-7, 14)
- ✓ 41.50 (2C) : four carbon at (C-10, 11)

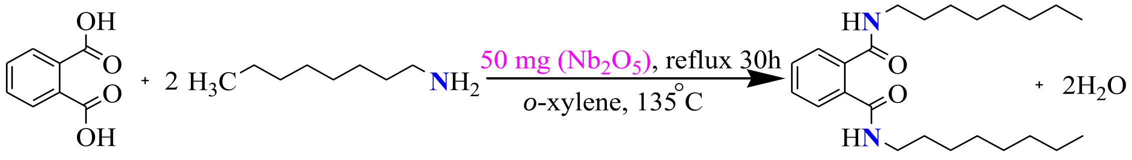
The total twenty (20) proton atoms and eighteen (18) carbons were obtained in the compound by ^{1}H-NMR and ^{13}C-NMR spectra. The spectral data of UV, FT-IR, and ^{1}H NMR and ^{13}C-NMR data are compatible with the structure of this compound shown as below:



2

3.9.3. Characterization of Synthesized *N, N*-dioctyl-phthalamide

The diamide-3 was synthesized by refluxing 1:2 molar ratios of phthalic acid (0.166g) and n-octylamine (0.33 mL) in *o*-xylene (4 mL) presence of 50 mg Nb_2O_5 heated around at 135 °C for in a sand bath 30 h with continuous stirring of magnetic bar at 300 rpm. The progress of the reaction was monitored by TLC with n-hexane (0.5 mL) and chloroform (2 mL).



3

After purification diamide-3 characterized by the following way:

A white solid was obtained molecular formula $C_{24}N_2O_2H_{40}$ with 92% yield, m.p 127-130 °C. The structure of the compound was established by various spectral analyses.

i) UV-visible spectroscopy:

The UV-visible spectrum (Fig. 3.9.3 (a), Page no. 63) of the diamide-3 showed the following peak:

- ✓ λ_{max} 242 nm: n→π* transition of C=O and presence of –NHR auxochrome.

ii) FT-infrared spectroscopy:

The FT-IR (KBr) spectrum (Fig.3.9.3 (b), Page no. 63) of the diamide-3 exhibited a number of bands, some of which were assigned as the follows at υ cm^{-1} :

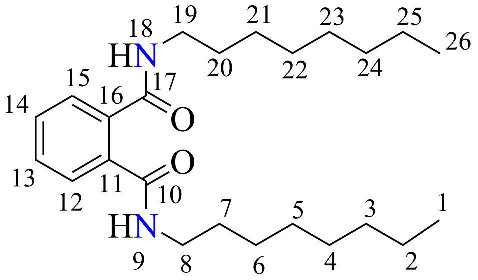
- ✓ 3238.59 : -NH str. of amide bond.
- ✓ 3078.49 : =C-H str. of aromatic
- ✓ 2929 : -C-H str. of $-CH_3$ (asy).
- ✓ 2856.67 : -C-H str. of $–CH_2$ (sym).
- ✓ 1627.97 : C=O str. for amide bond.
- ✓ 1544 : -NH bend.
- ✓ 1457 : C=C aromatic.
- ✓ 1426.41 : $-CH_2$ bend.
- ✓ 1317.43 : $-CH_3$ bend.
- ✓ 1155 : -C-N bend.
- ✓ 1166.67 : -C-O bend.

iii) ^{1}H-NMR spectroscopy:

The ^{1}H-NMR spectrums (Fig.3.9.3 (c), Page no. 64) of the diamide-3 exhibited signals (in δ ppm) which were assigned as follows:

- ✓ 7.60-7.58, 7.47-7.45 (m, 4H) : four aromatic protons (C-12, 13, 14, 15)
- ✓ 6.78 (br s, 2H, -NH)) : two protons of two amide bond at (N-9, 18)
- ✓ 3.41-3.36 (m, 4H) : four protons at (C-8, C-19)
- ✓ 1.78 (m, 4H) : four protons at (C-7, 20)
- ✓ 1.62-1.55 (m, 4H) : four protons at (C-6, C-21)
- ✓ 1.34-1.29 (m, 16H) : twenty protons at (C-2-6, C-21-25)
- ✓ 0.91-0.86 (t, *J* =6.40 Hz, 6H) : six protons at (C-1, C-26).

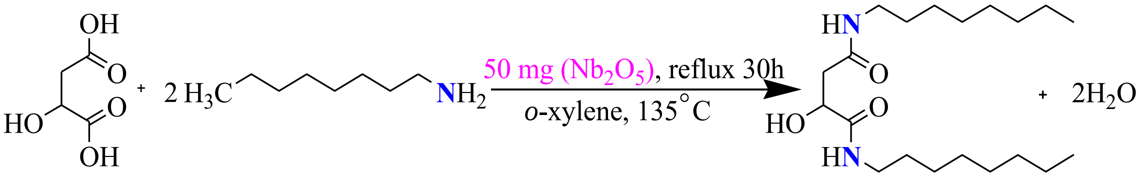
The total forty (40) proton atoms were obtained in the compound by ^{1}H-NMR.The spectral data of UV, FT-IR, and ^{1}H-NMR data are compatible with the structure of this compound shown as below:



3

3.9.4. Characterization of Synthesized *N, N*-dioctyl-2-hydroxy-butanediamide

The diamde-4 was synthesized by refluxing 1:2 molar ratios of DL-malic acid (0.135g) and n-octylamine (0.33 mL) in *o*-xylene (4 mL) presence of 50 mg Nb_2O_5 heated around at 135 °C for 30 h in a sand bath with continuous stirring of magnetic bar at 300 rpm. The progress of the reaction was monitored by TLC with n-hexane (2 mL) and chloroform (0.5 mL).



4

After purification diamide-4 characterized by the following way:

A yellowish solid was obtained molecular formula $C_{20}N_2O_3H_{40}$ with 70% yield, m.p 150-152 °C. The structure of the compound was established by various spectral analyses.

i) UV-visible spectroscopy:

The UV-visible spectrum (Fig. 3.9.4 (a), Page no. 67) of the diamide-4 showed the following peak:

- ✓ λ_{max} 383.50 nm : n→π* transition of C=O and presence of –NHR, OH auxochrome.

ii) FT-infrared spectroscopy:

The FT-IR (KBr) spectrum (Fig. 3.9.4. (b), Page no. 67) of the dimaide-4 exhibited a number of bands, some of which were assigned as the follows at υ cm^{-1} :

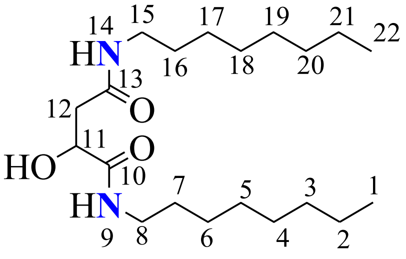
- ✓ 3295.49 : -NH str. of amide bond.
- ✓ 3102.6 : Overtone of –NH bending.
- ✓ 2921.29 : -C-H str. of -CH_3 (asy).
- ✓ 2852.81 : -C-H str. of –CH_2 (sym).
- ✓ 1645.33 : C=O str. for amide bond.
- ✓ 1567.21 : -NH bend.
- ✓ 1436 : -CH_2 bend.
- ✓ 1334.78 : -CH_3 bend.
- ✓ 1287.15 : -C-N bend.
- ✓ 1189.53 : -C-O bend.

iii) ^{1}H-NMR spectroscopy:

The ^{1}H-NMR spectrums (Fig.3.9.4 (c), Page no. 68) of the diamide-4 exhibited signals (in δ ppm) which were assigned as follows:

- ✓ 7.06 (br s, 1H, -NH) : one proton amide bond at (N-9)
- ✓ 6.37 (br s, 1H, -NH)) : one proton of amide bond at (N-14)
- ✓ 4.38-4.36 (m, 1H, -OH) : one proton of –OH at (C-11)
- ✓ 3.29-3.22 (m, 4H) : four protons at (C-8, C-15)
- ✓ 2.80-2.76 (m, 1H) : one proton at (C-11)
- ✓ 2.66-2.60 (m, 2H) : two protons at (C-12)
- ✓ 1.53-1.49 (m, 4H) : four protons at (C-6, C-17)
- ✓ 1.29-1.28 (m, 20H) : tweenty protons at (C:2-6, C:17-21)
- ✓ 0.91-0.88 (t, *J*=6.40 Hz, 6H) : six protons at (C-1, C-22).

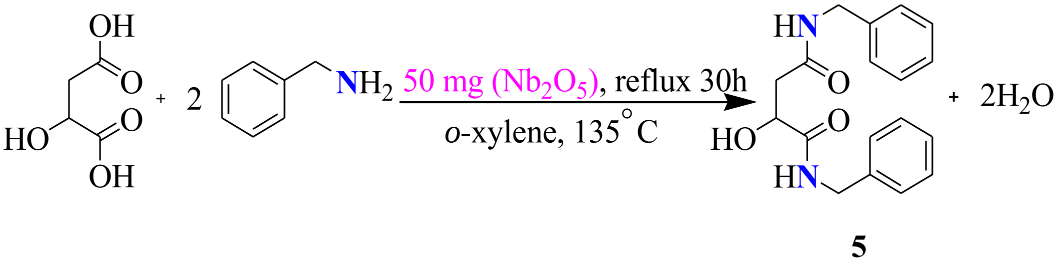
The total forty (40) proton atoms were obtained in the diamide-4 by ^{1}H-NMR spectra. The spectral data of UV, FT-IR, and ^{1}H-NMR data are compatible with the structure of this compound shown as below:



4

3.9.5. Characterization of Synthesized *N, N*-dibenzyl-2-hydroxy-butanediamide

The diamide-5 was synthesized by refluxing 1:2 molar ratios of DL-malic acid (0.135g) and benzylamine (0.22 mL) in *o*-xylene (4 mL) presence of 50 mg Nb_2O_5 heated around at 135 °C for 30 h in a sand bath with continuous stirring of magnetic bar at 300 rpm. The progress of the reaction was monitored by TLC with n-hexane (2 mL) and chloroform (1 mL).



5

After purification diamide-5 characterized by the following way:

A white solid was obtained molecular formula $C_{18}N_2O_3H_{20}$ with 63% yield, m.p 146-150 °C. The structure of the compound was established by various spectral analyses.

i) UV-visible spectroscopy:

The UV-visible spectrum (Fig. 3.9.5 (a), Page no. 70) of the diamide-5 showed the following peak:

- ✓ λ_{max} 253 nm: n→π* transition of C=O, presence of –NHR and -OH auxochrome.

ii) FT-infrared spectroscopy:

The FT-IR (KBr) spectrum (Fig.3.9.5 (b), Page no. 70) of the diamide-5 exhibited a number of bands, some of which were assigned as the follows at υ cm^{-1}:

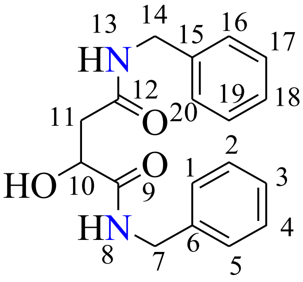
- ✓ 3338.93 : -NH str. of amide bond.
- ✓ 3037.99 : =C-H str. of aromatic.
- ✓ 2929.97 : -C-H str. of $–CH_2$ (assy).
- ✓ 1649.26 : C=O str. for amide bond.
- ✓ 1543.10 : -NH bend.
- ✓ 1459 : C=C of aromatic
- ✓ 1426.41 : $-CH_2$ bend.
- ✓ 1284.63 : -C-N bend.
- ✓ 1085.96 : -C-O bend.

iii) ^{1}H-NMR spectroscopy:

The ^{1}H-NMR spectrums (Fig.3.9.5 (c), Page no. 71) of the diamide-5 exhibited signals (in δ ppm) which were assigned as follows:

- ✓ 7.39-7.25 (m, 10H) : ten protons of two Ar. groups (C:1-5; 16-20)
- ✓ 6.74 (br s, 2H, -NH) : two protons of two amide bond at (N-8, 13)
- ✓ 4.43-4.42 (m, 4H) : four protons at (C-7, C-14)
- ✓ 2.89-2.84 (m, 1H) : one proton at (C-10)
- ✓ 2.72-2.66 (m, 2H) : two proton at (C-11)
- ✓ 1.93 (m, -OH, 1H) : one proton of -OH at (C-10)

The total twenty (20) proton atoms were obtained in the diamide-5 by ^{1}H-NMR spectra. The spectral data of UV, FT-IR, and ^{1}H-NMR data are compatible with the structure of this compound shown as below:



5

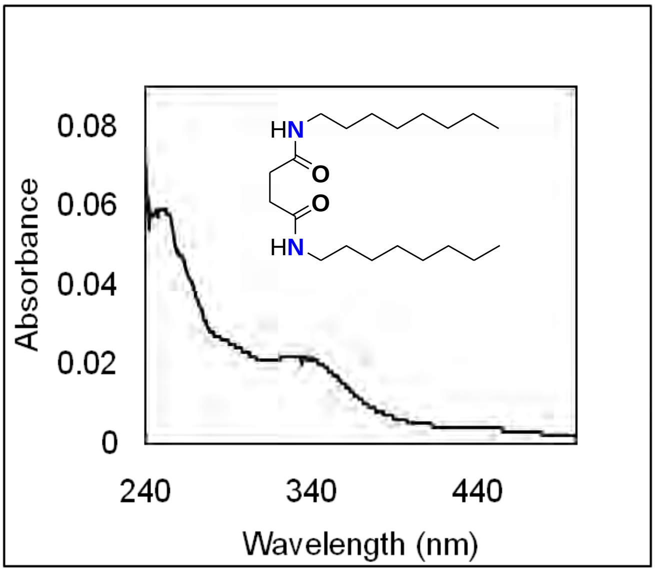


Fig. 3.9.1 (a): UV-Vis spectrum of diamide-1.

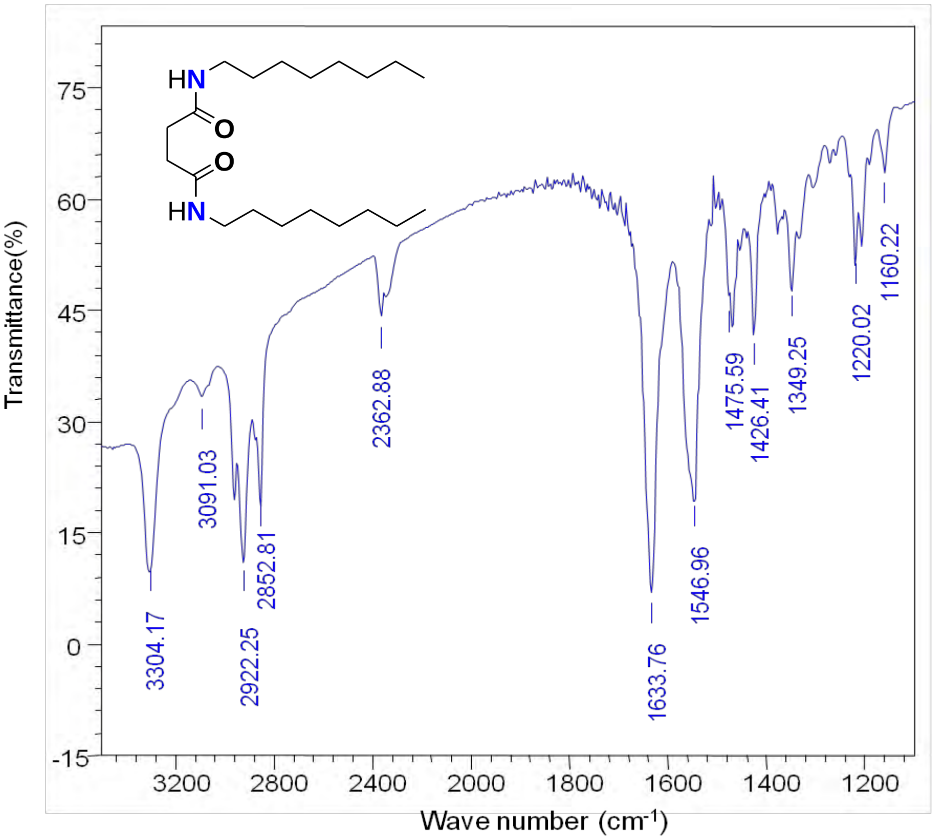


Fig. 3.9.1 (b): FR- IR spectrum of diamide-1.

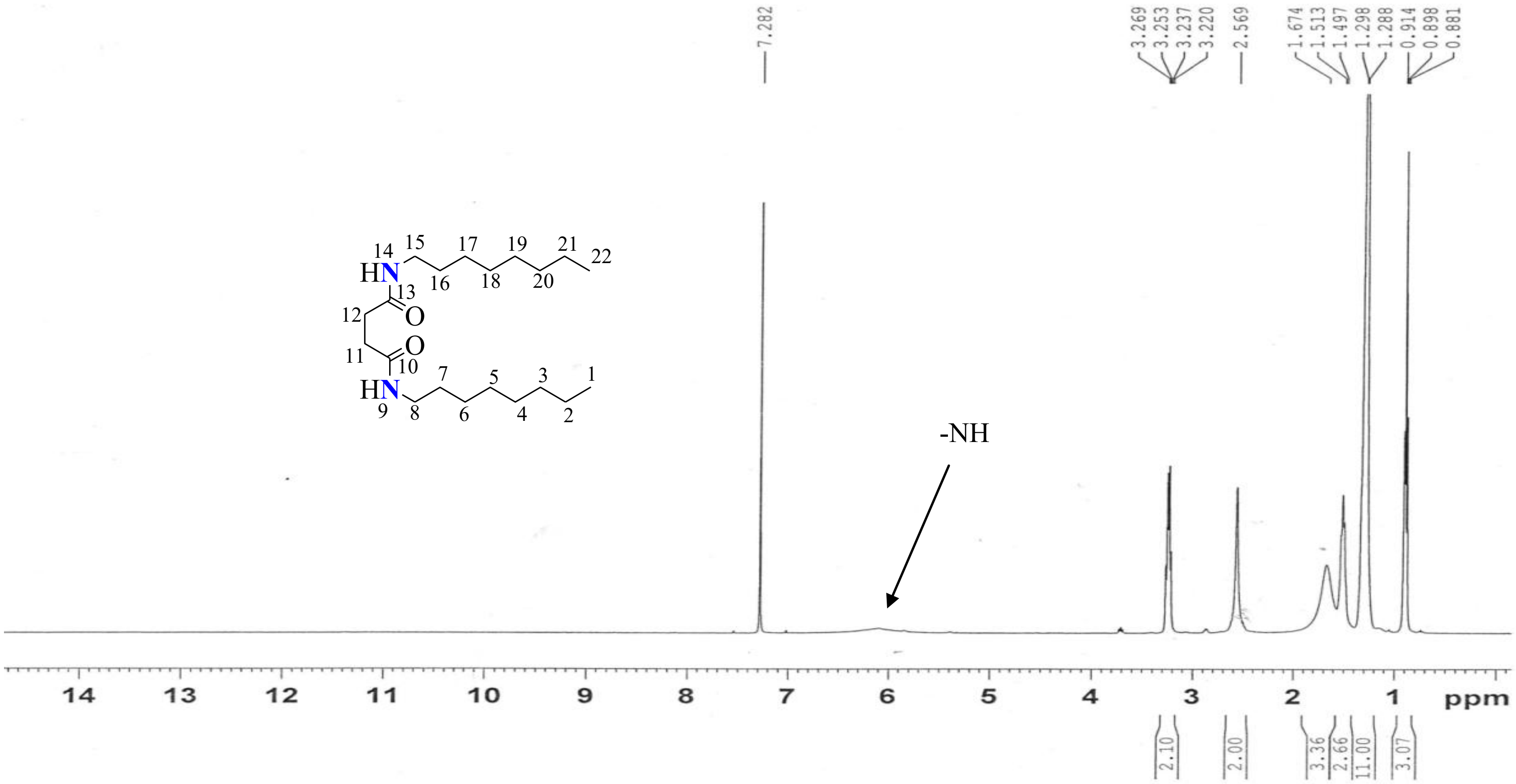


Fig. 3.9.1 (c): ^{1}H-NMR spectrum of diamide-1.

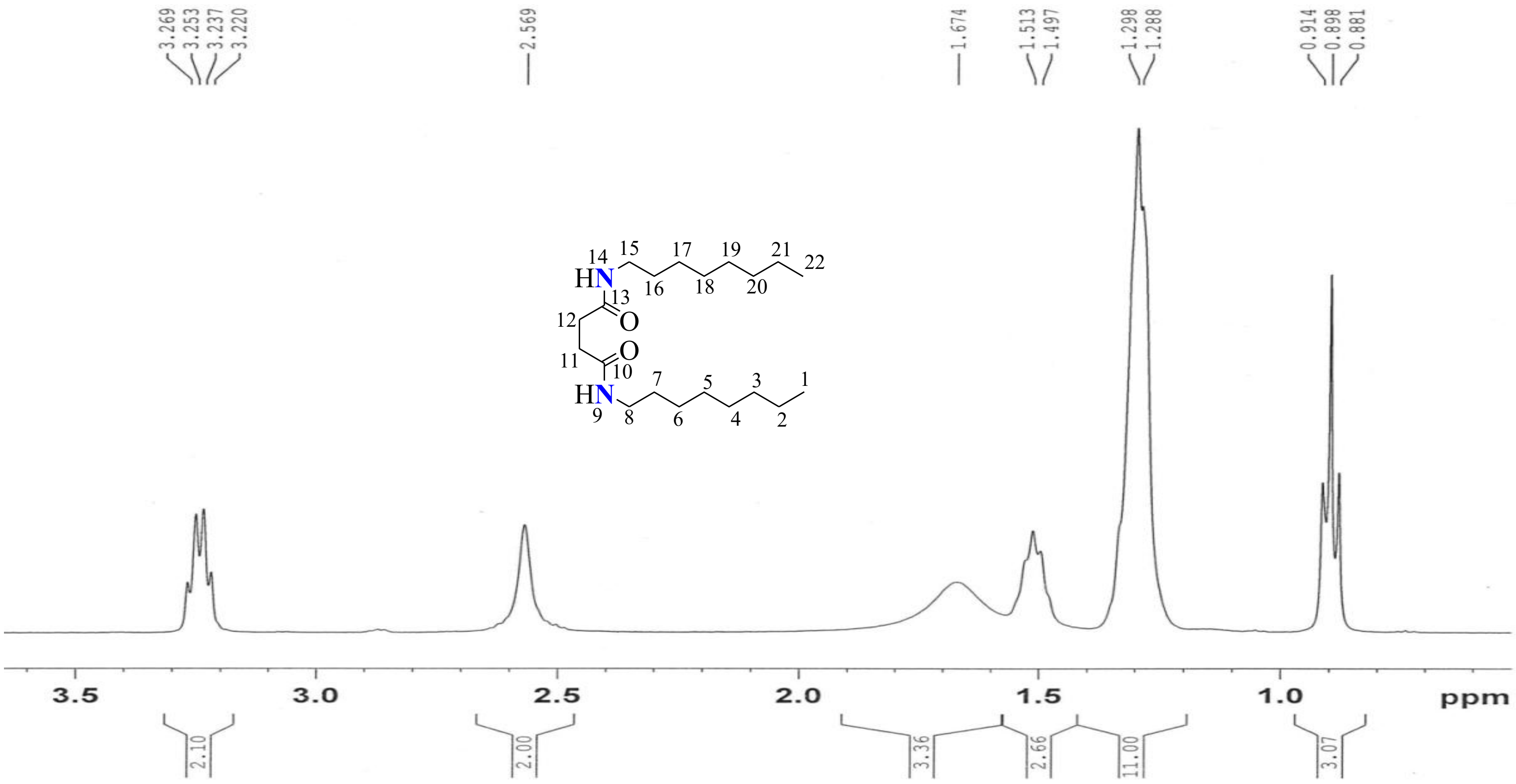


Fig. 3.9.1 (d): Extended ^{1}H-NMR spectrum of diamide-1.

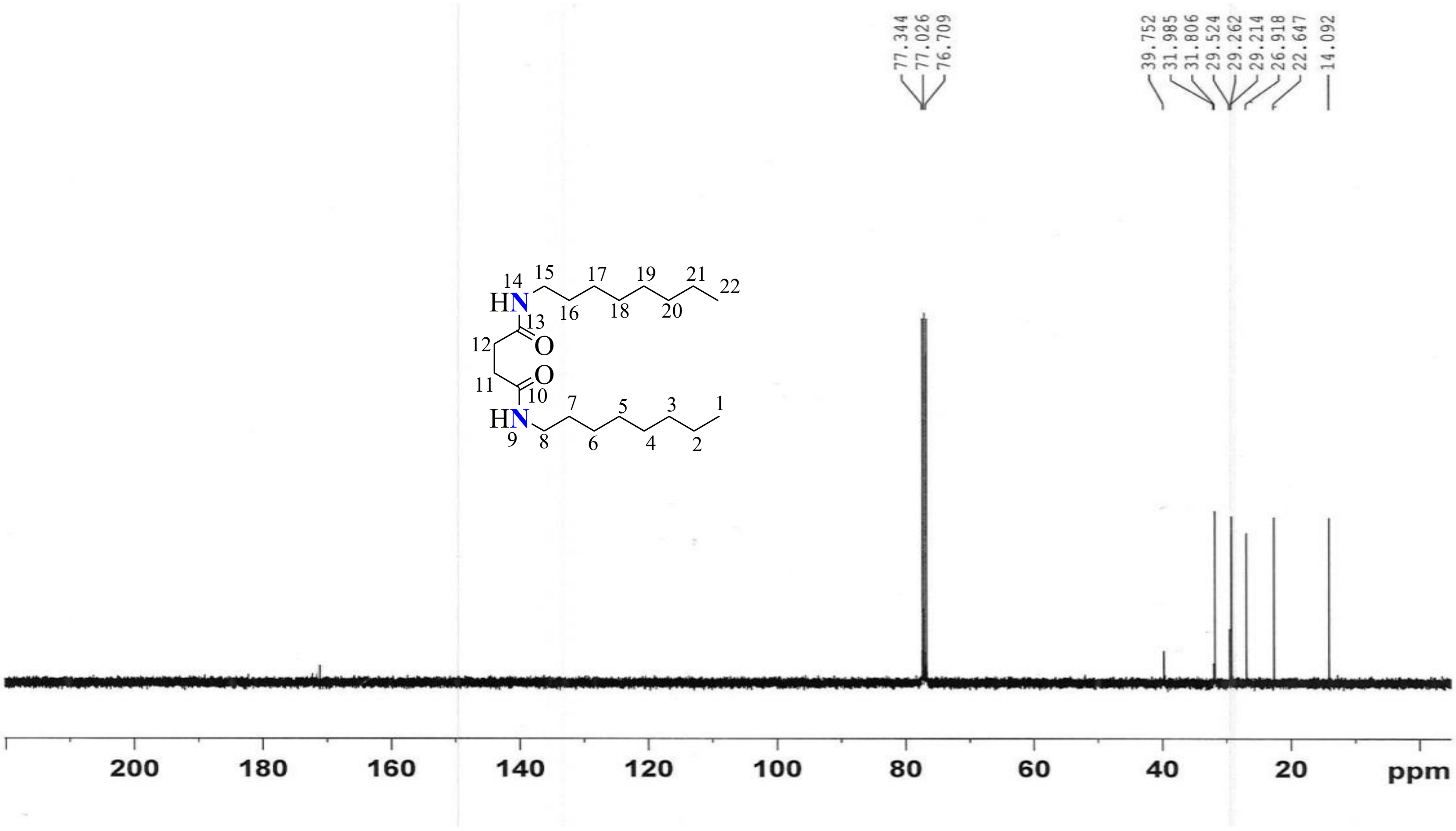


Fig. 3.9.1 (e): ^{13}C-NMR spectrum of diamide-1.

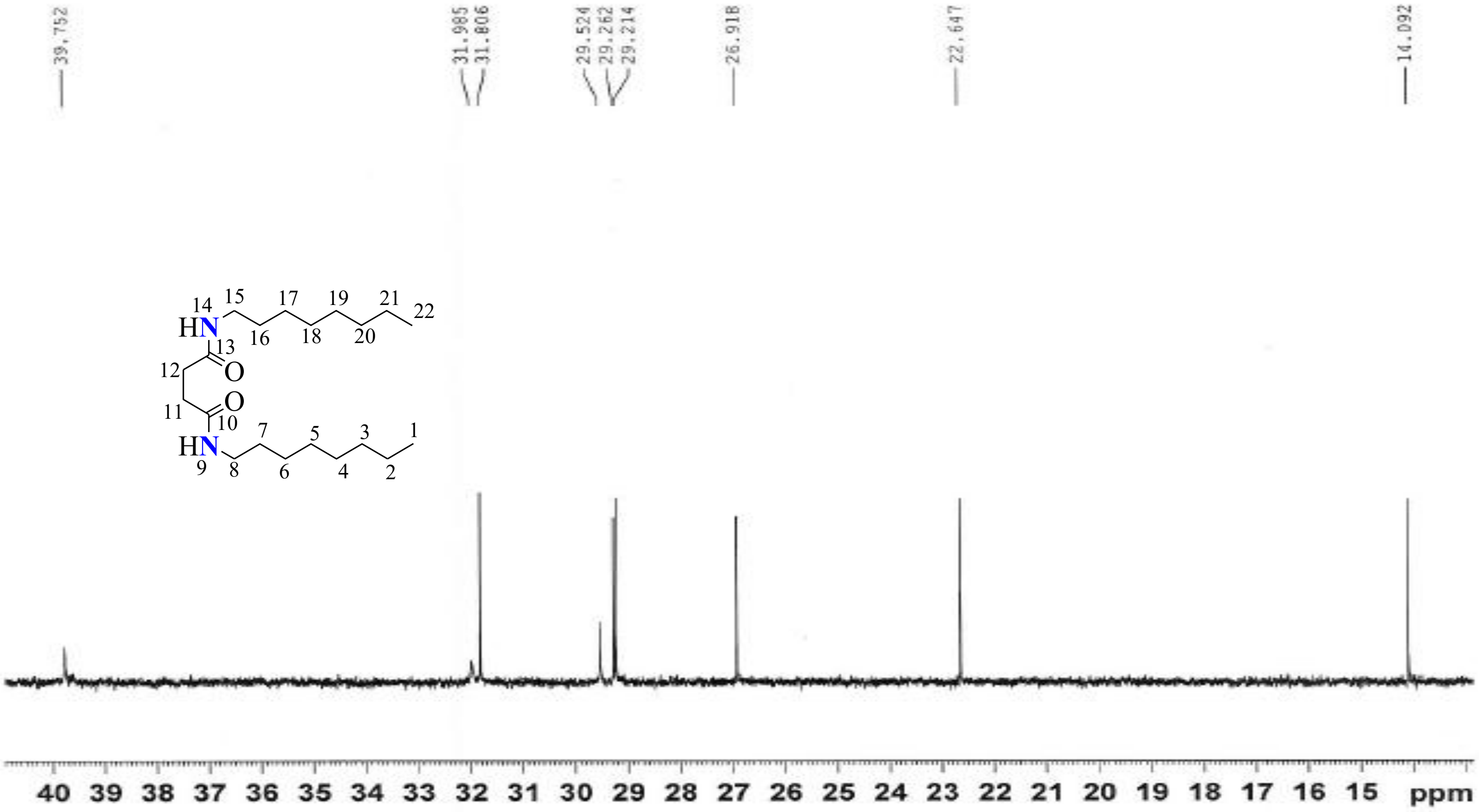


Fig. 3.9.1 (f): Extended ^{13}C-NMR spectrum of diamide-1.

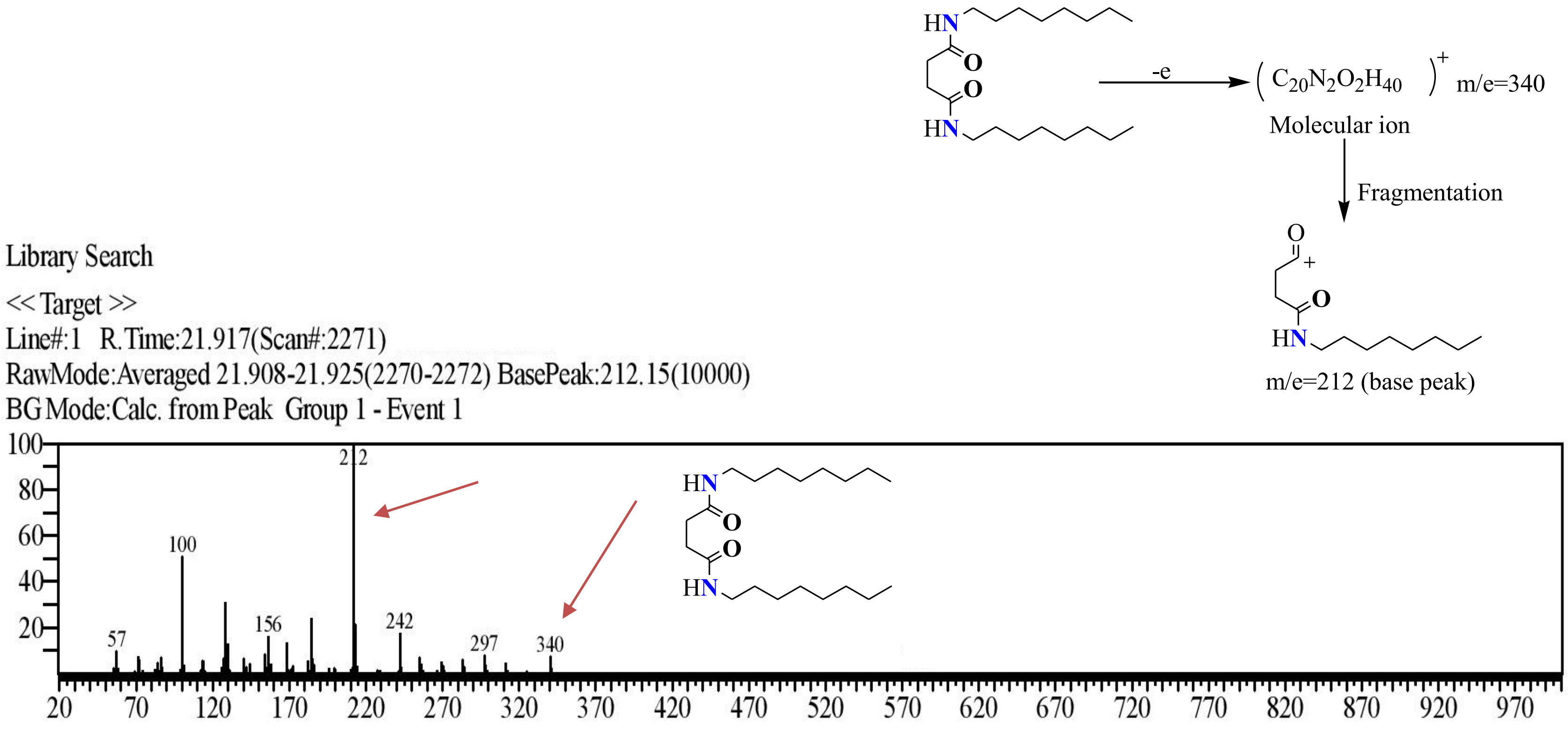


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Fig. 3.9.1 (g): GC-MS spectrum of diamide-1.

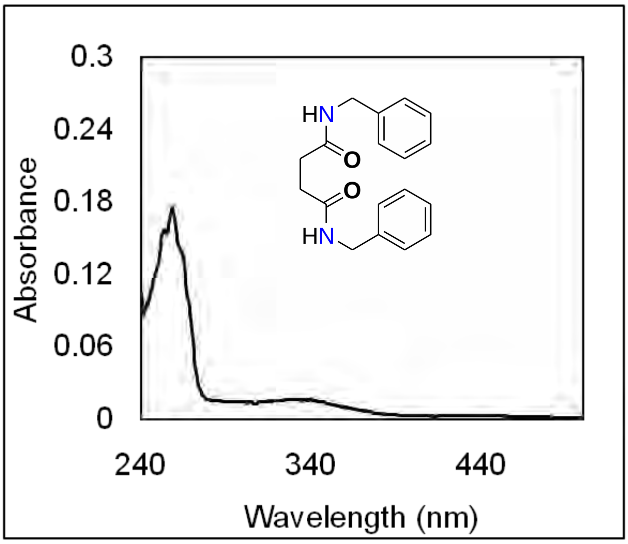


Fig.3.9.2 (a): UV-Vis spectrum of diamide-2.

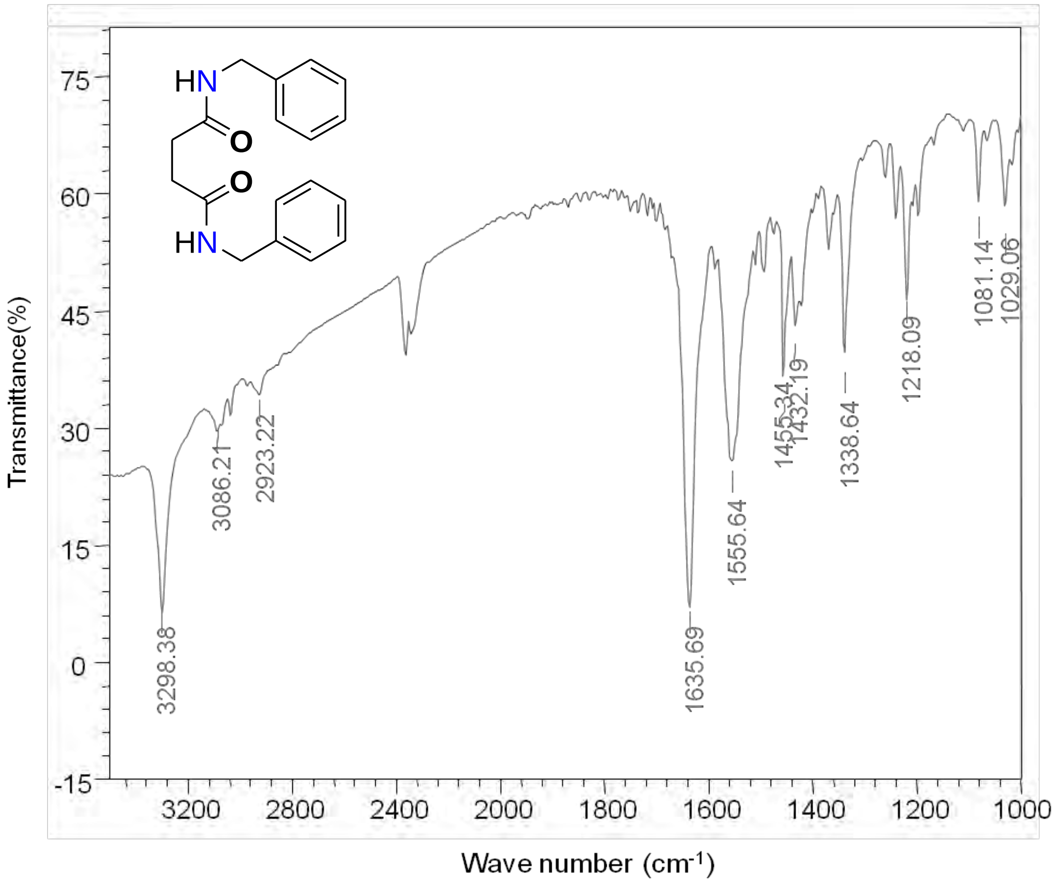


Fig.3.9.2 (b): FT-IR spectrum of diamide-2.

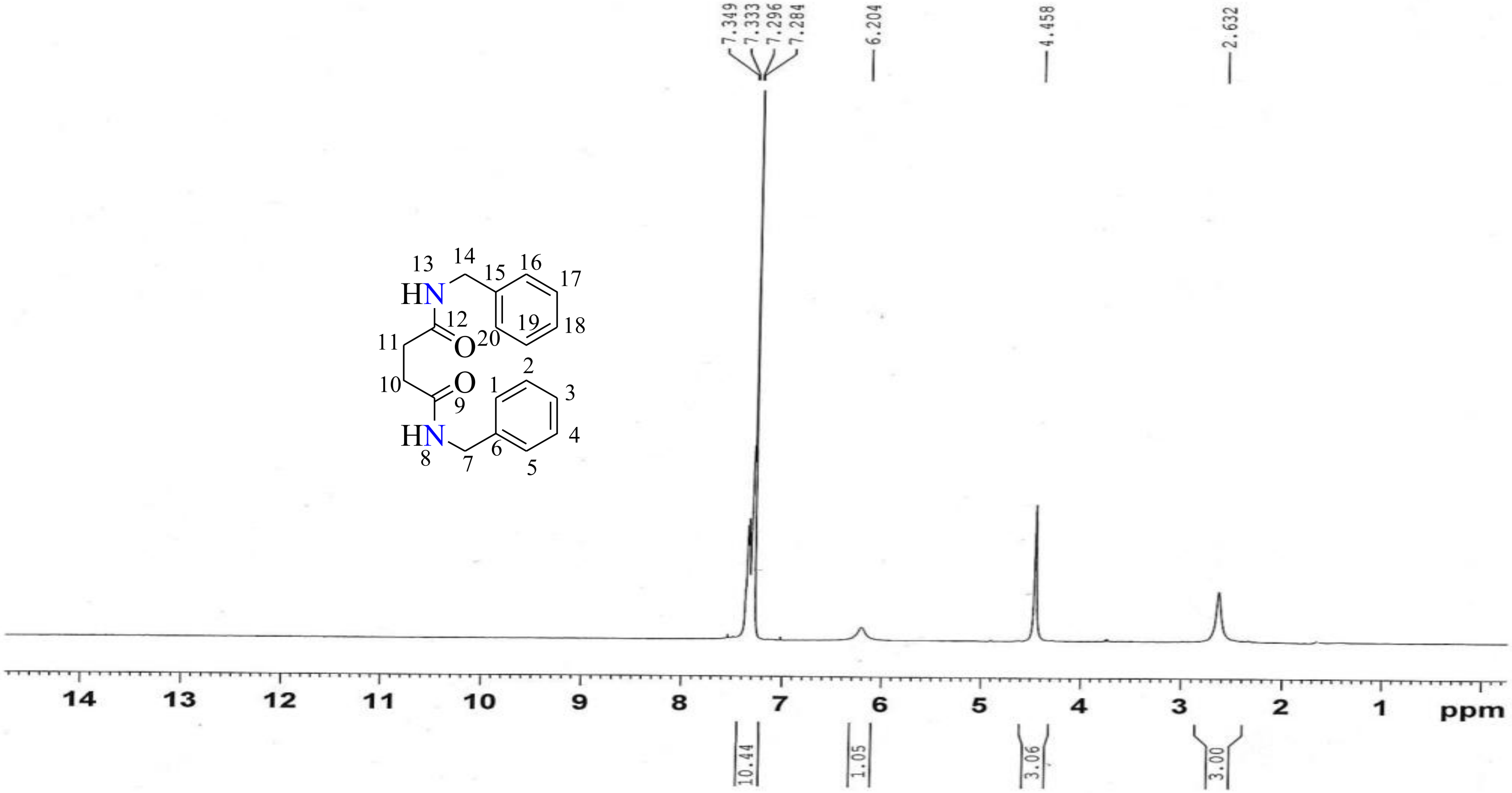


Fig. 3.9.2 (c): ^{1}H-NMR spectrum of diamide-2.

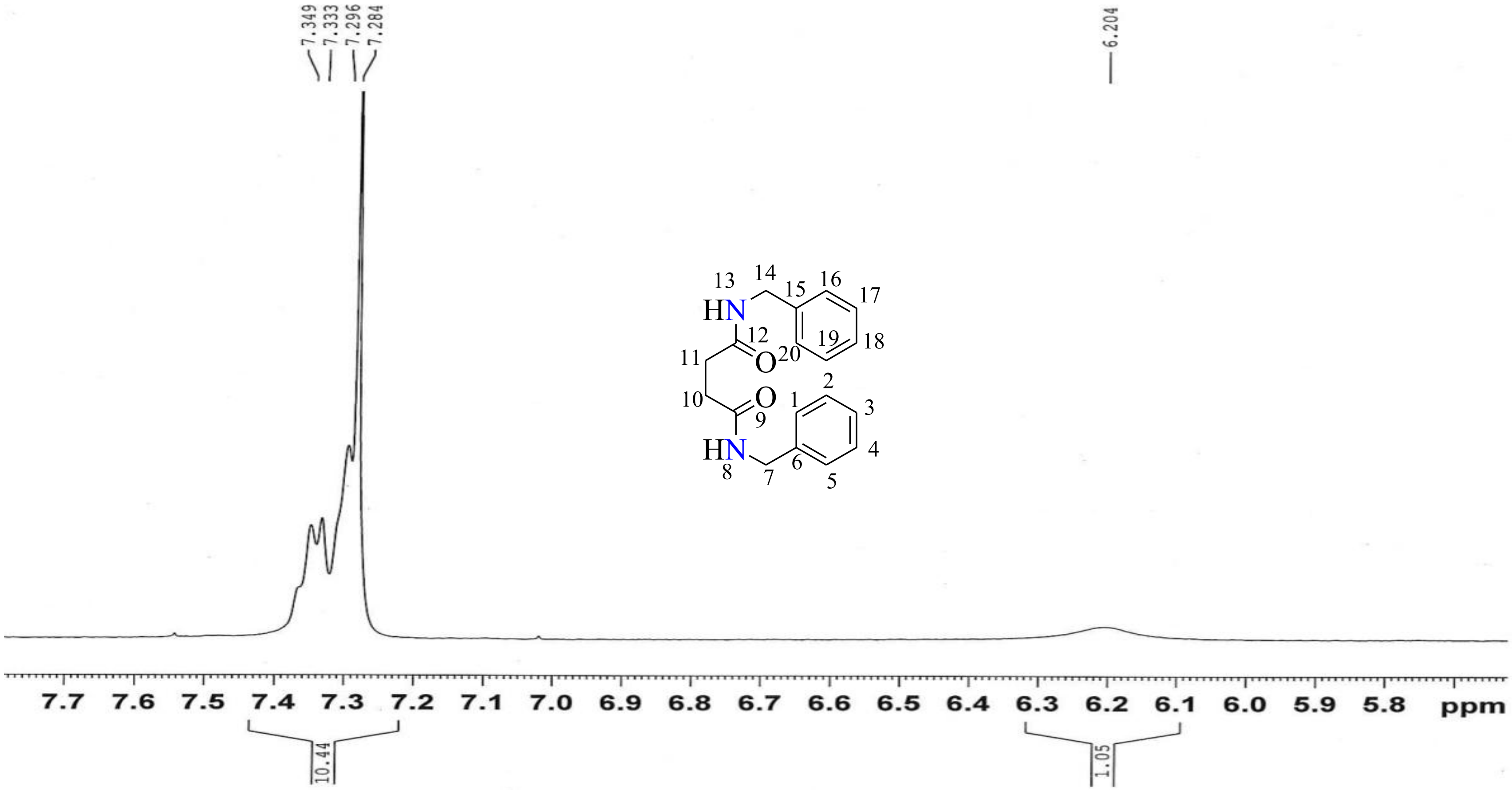


Fig. 3.9.2 (d): Extended ^{1}H-NMR spectrum of diamide-2.

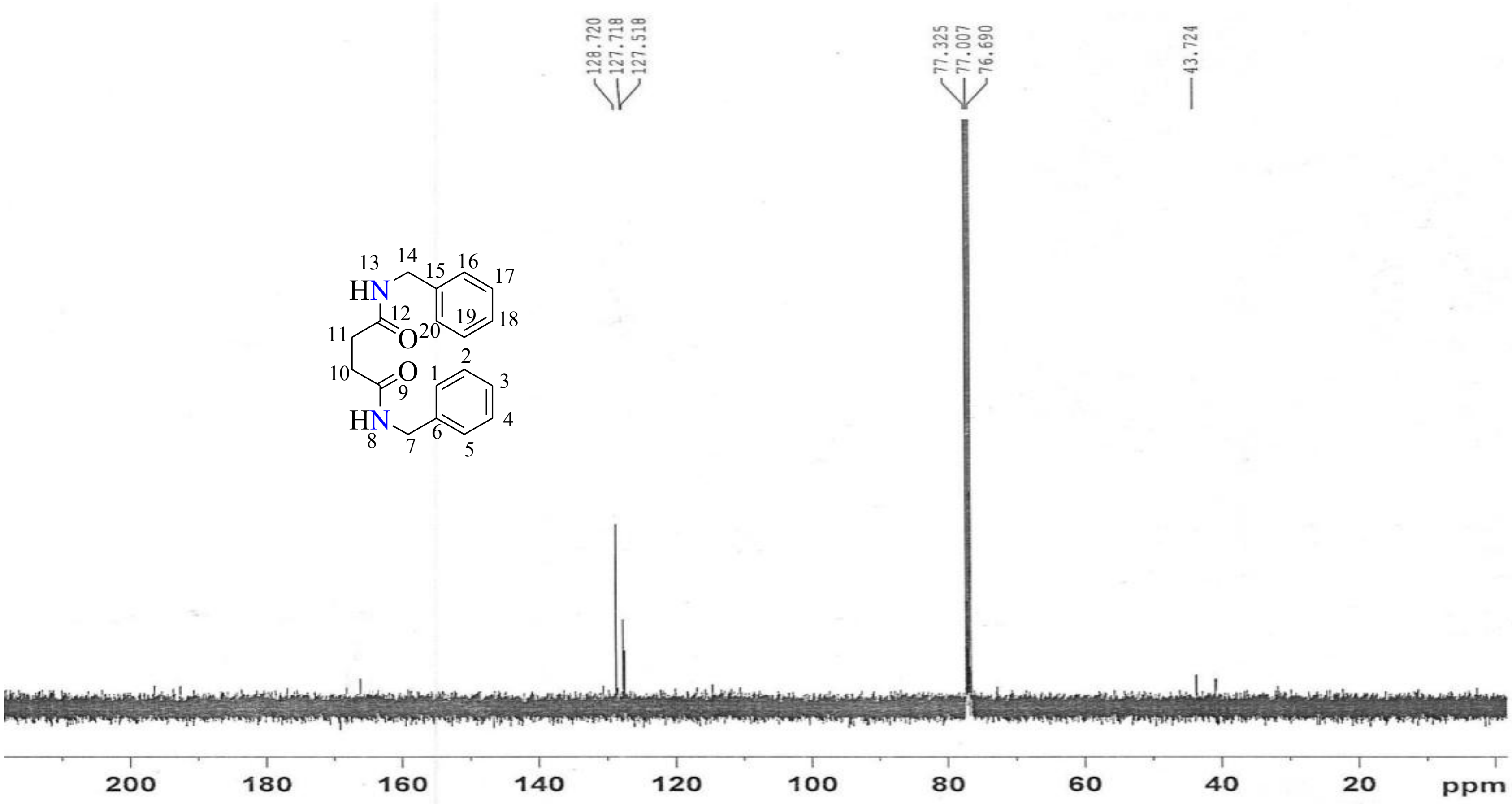


Fig.3.9.2 (e): ^{13}C-NMR spectrum of diamide-2.

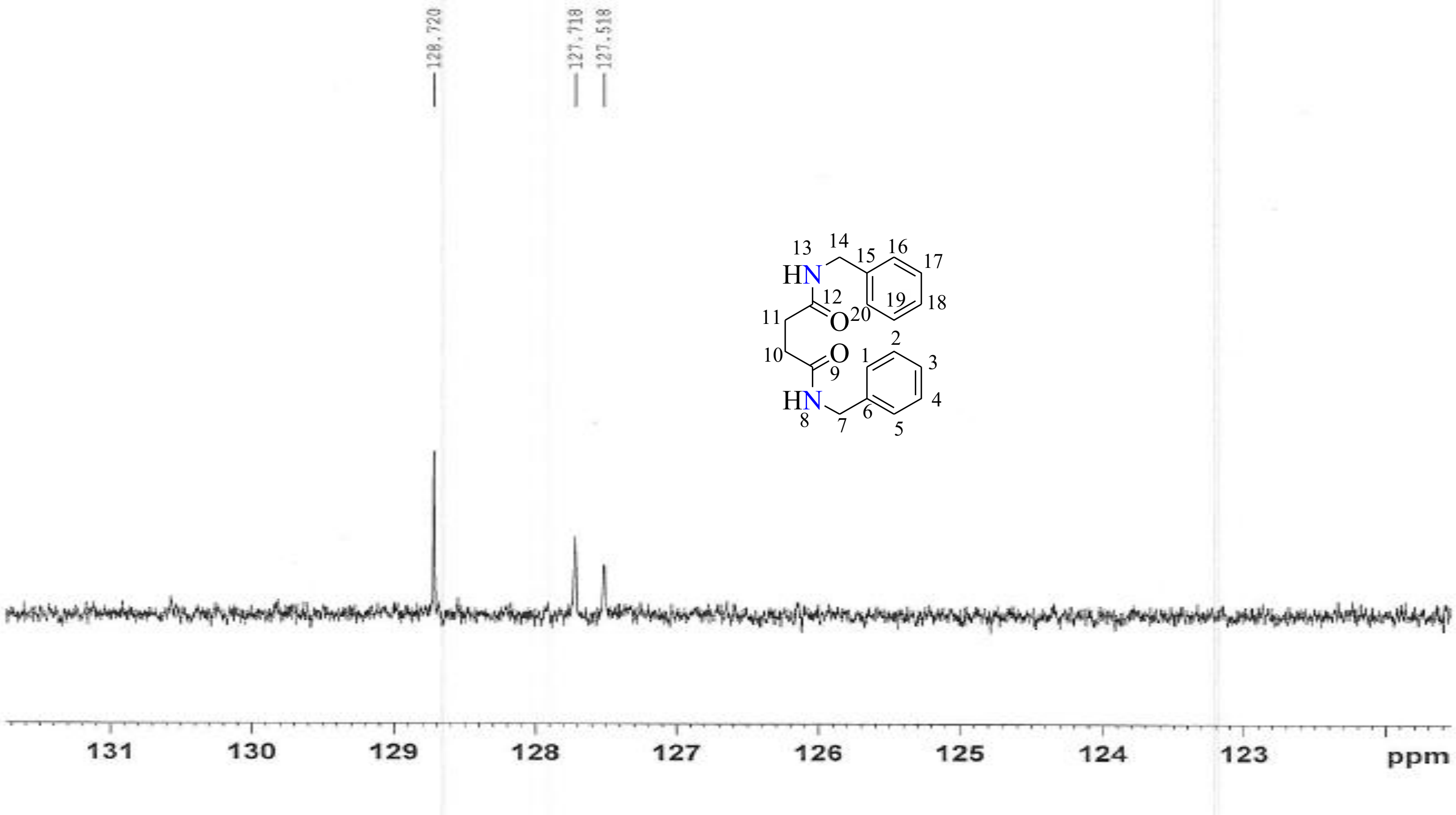


Fig. 3.9.2 (f): Extended ^{13}C-NMR spectrum of diamide-2.

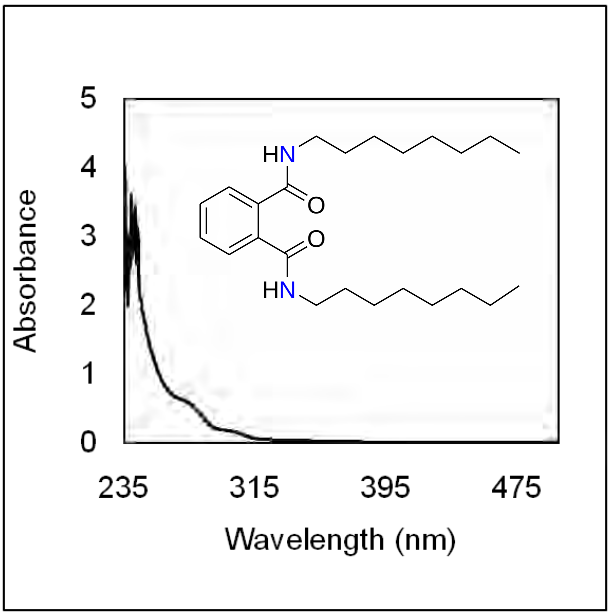


Fig. 3.9.3 (a): UV-Vis spectrum of diamide-3.

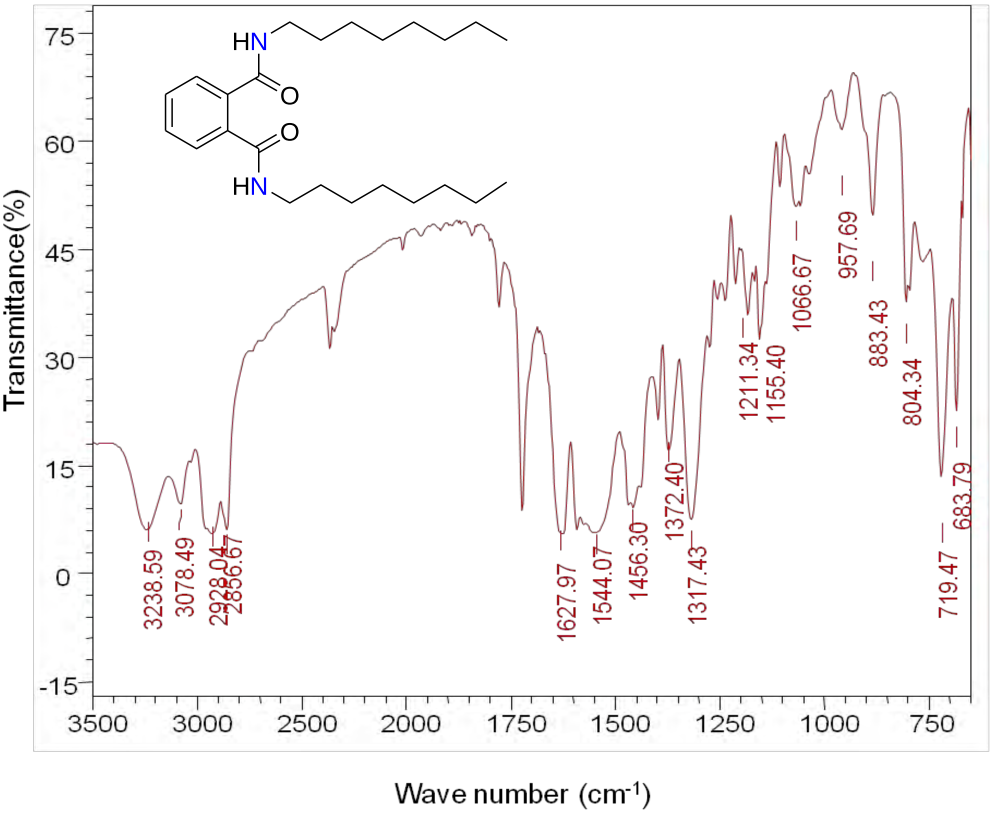


Fig.3.9.3 (b): FT-IR spectrum of diamide-3.

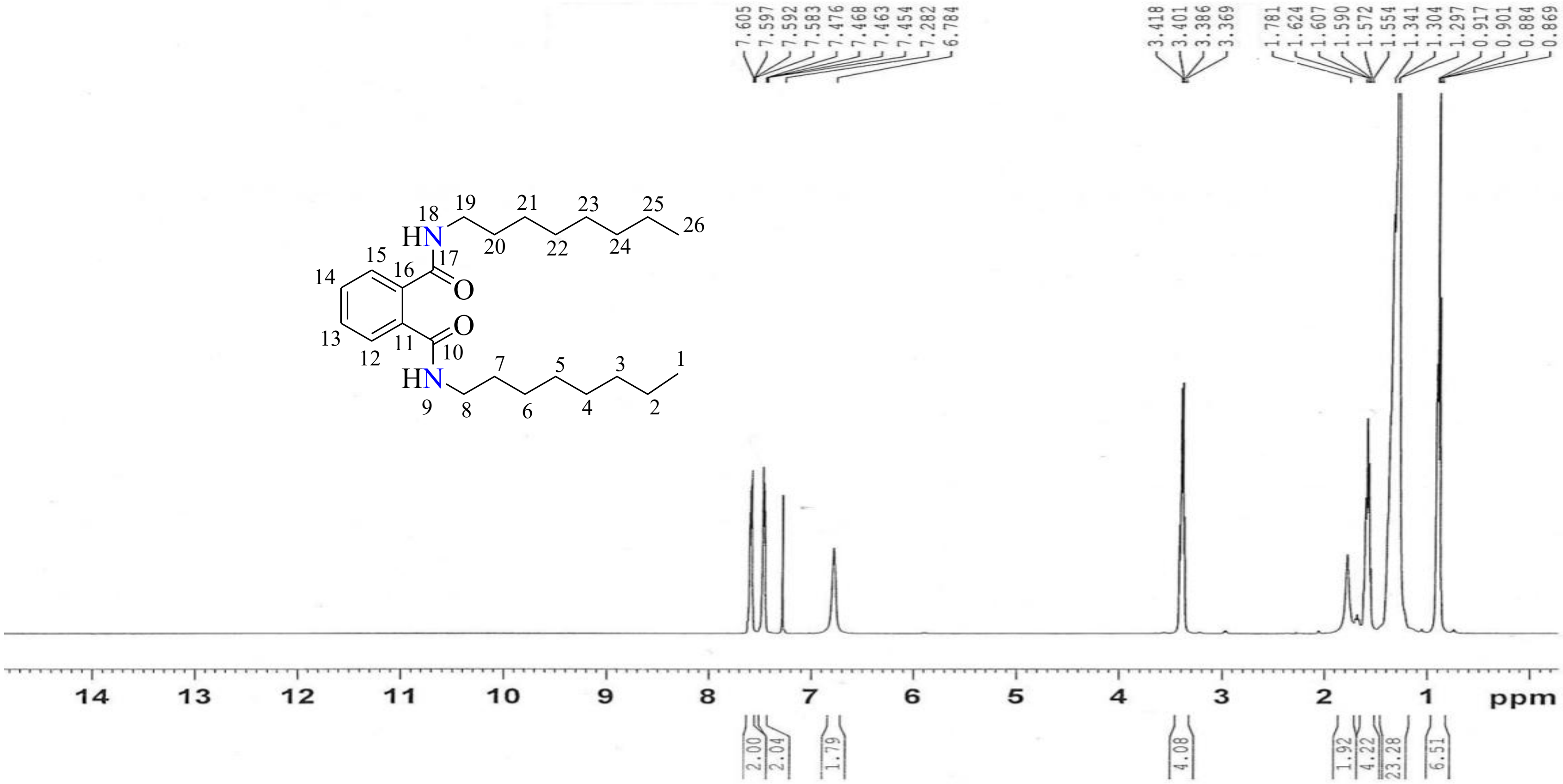


Fig. 3.9.3 (c): ^{1}H-NMR spectrum of diamide-3.

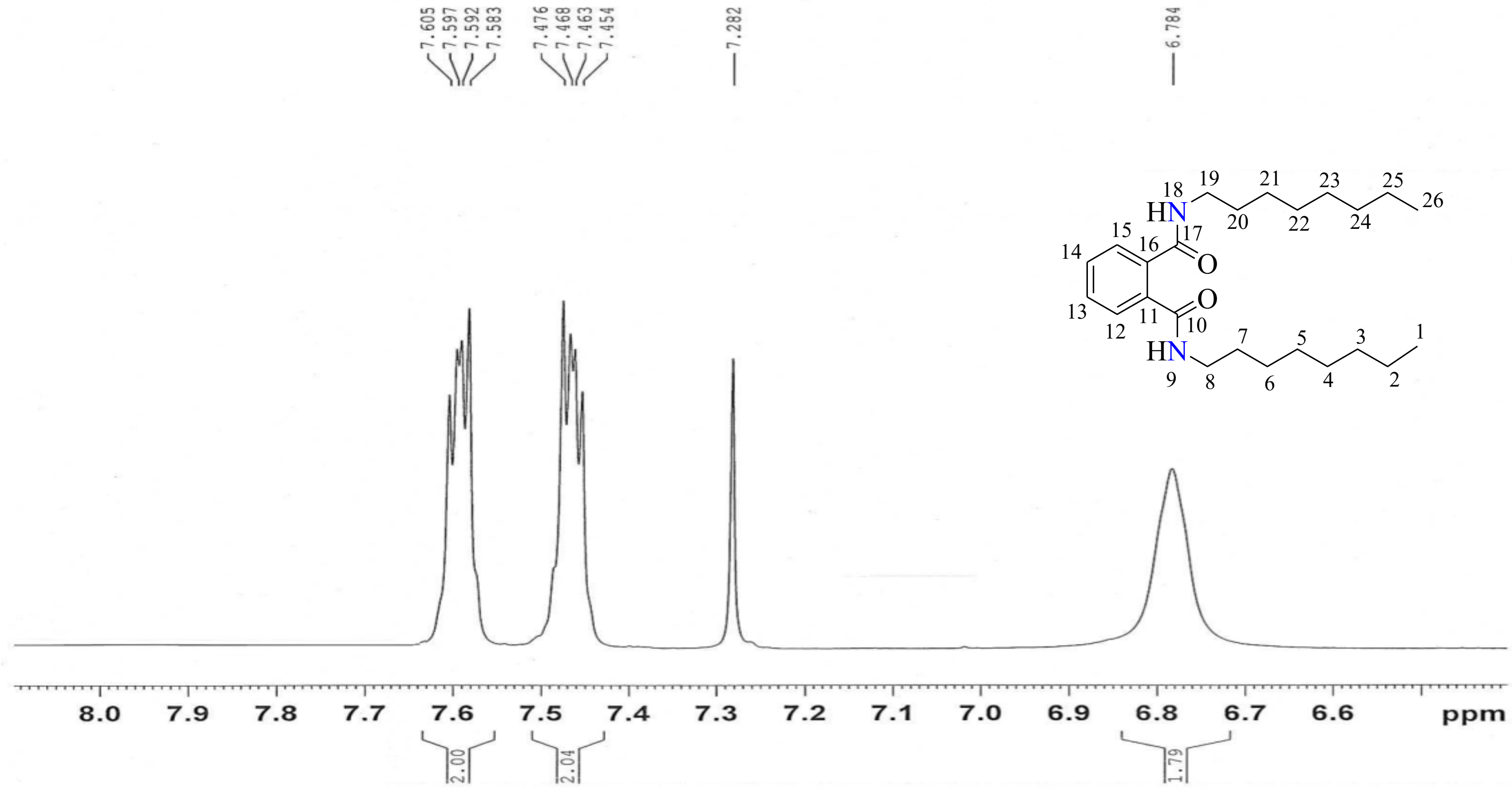


Fig. 3.9.3 (d): Extended ^{1}H-NMR spectrum of diamide-3.

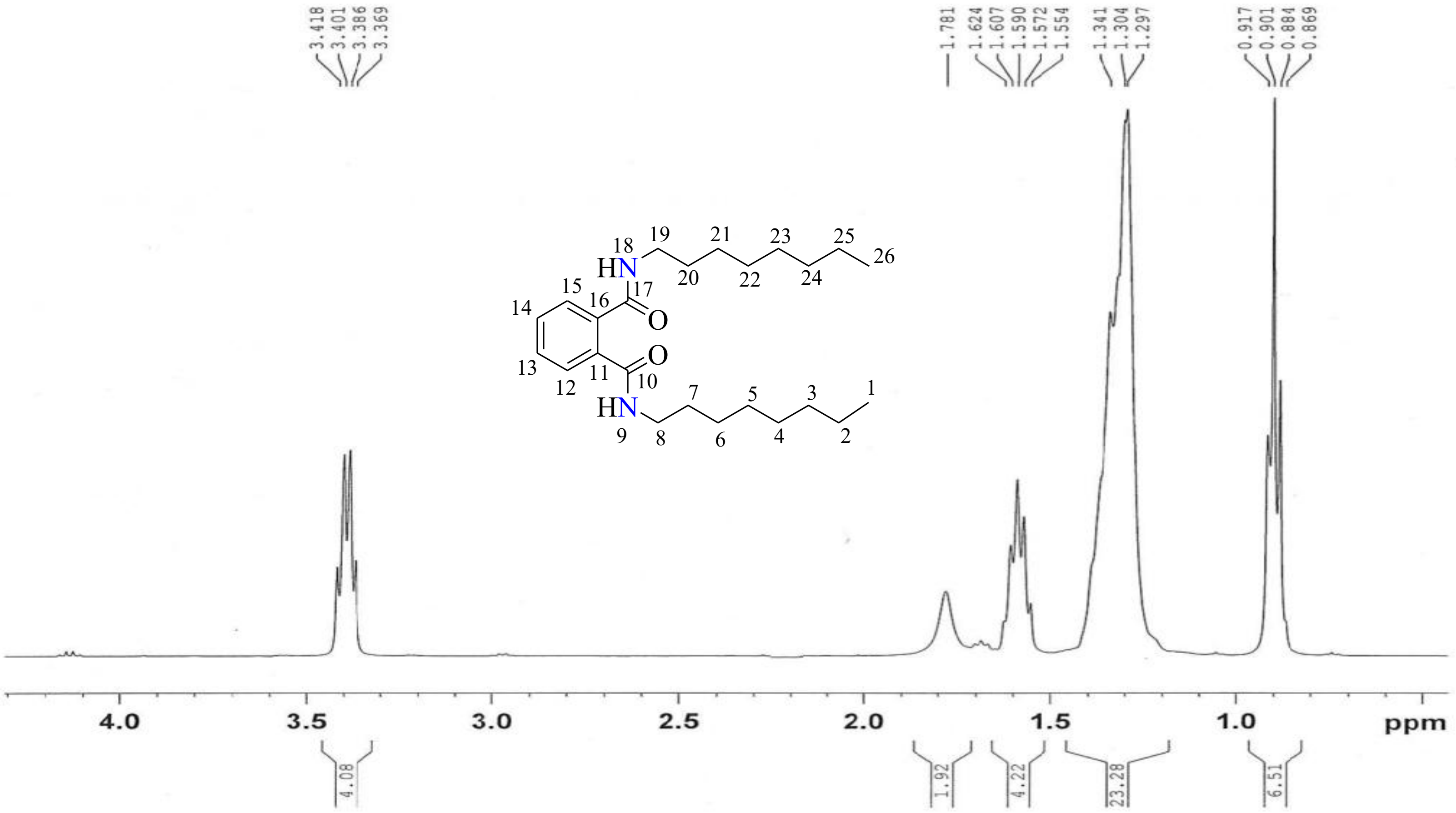


Fig. 3.9.3 (e): Extended ^{1}H-NMR spectrum of diamide-3.

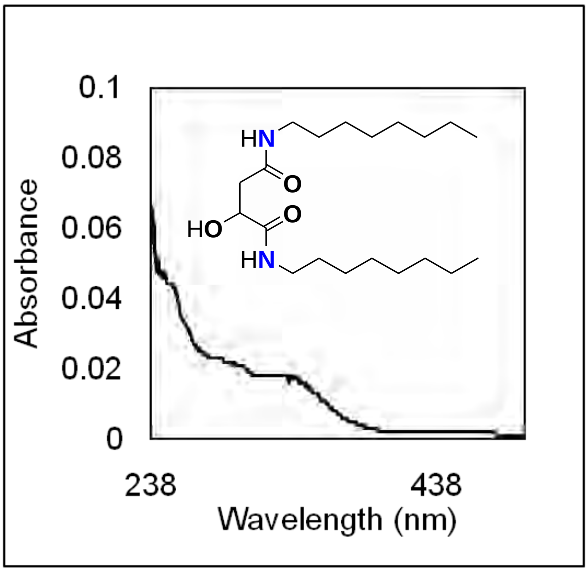


Fig. 3.9.4 (a): UV-Vis spectrum of diamide-4.

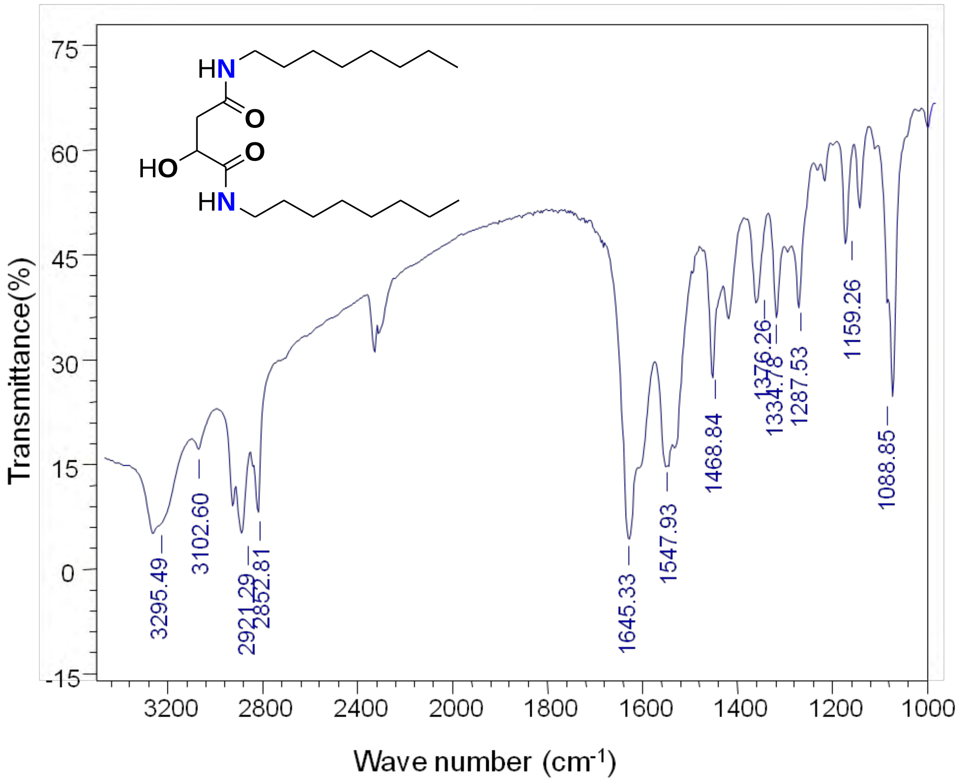


Fig. 3.9.4 (b): FT-IR spectrum of diamide-4.

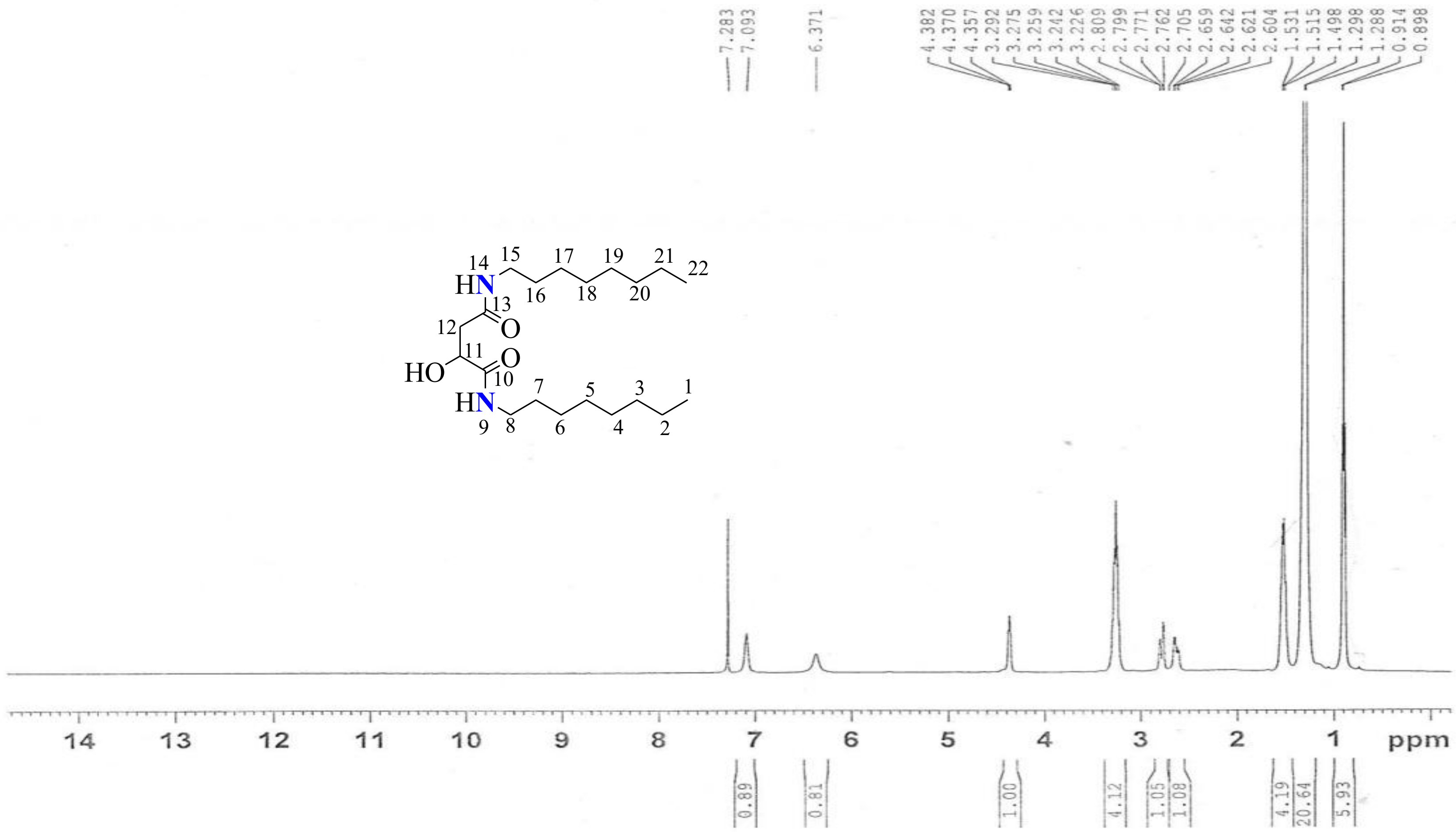


Fig. 3.9.4 (c): ^{1}H-NMR spectrum of diamide-4.

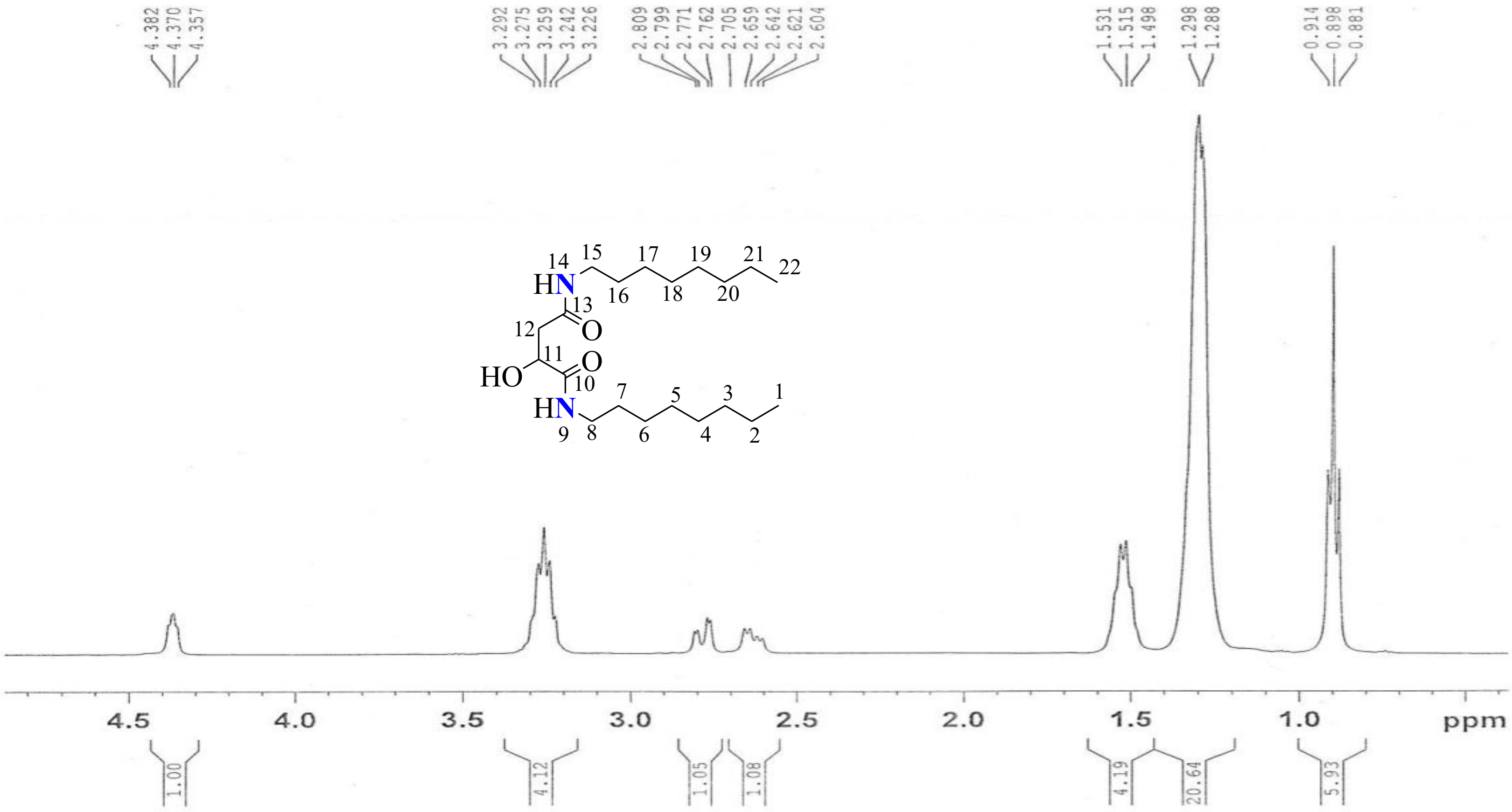


Fig. 3.9.4 (d): Extended ^{1}H-NMR spectrum of diamide-4.

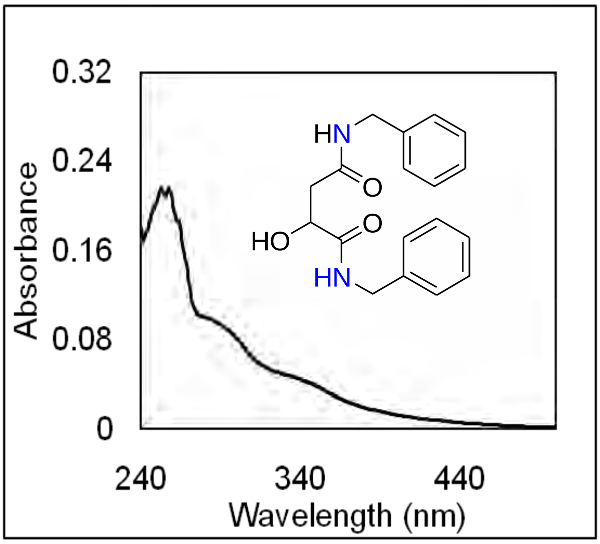


Fig.3.9.5 (a): UV-Vis spectrum of diamide-5.

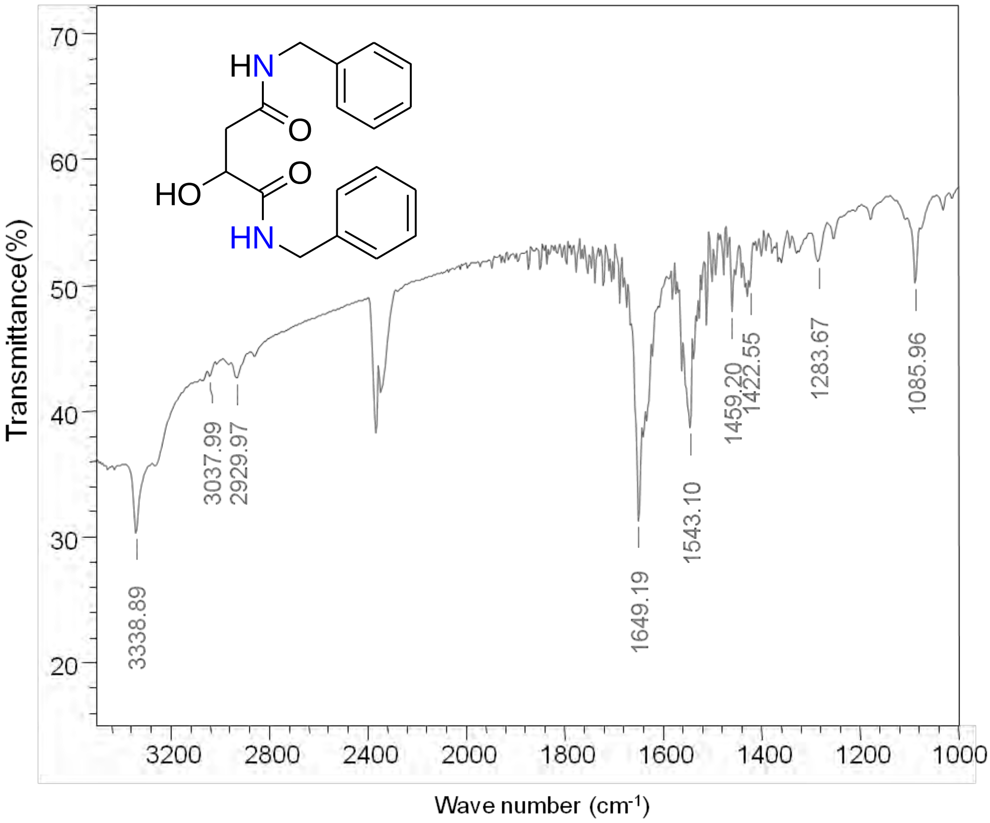


Fig. 3.9.5 (b): FT-IR spectrum of diamide-5.

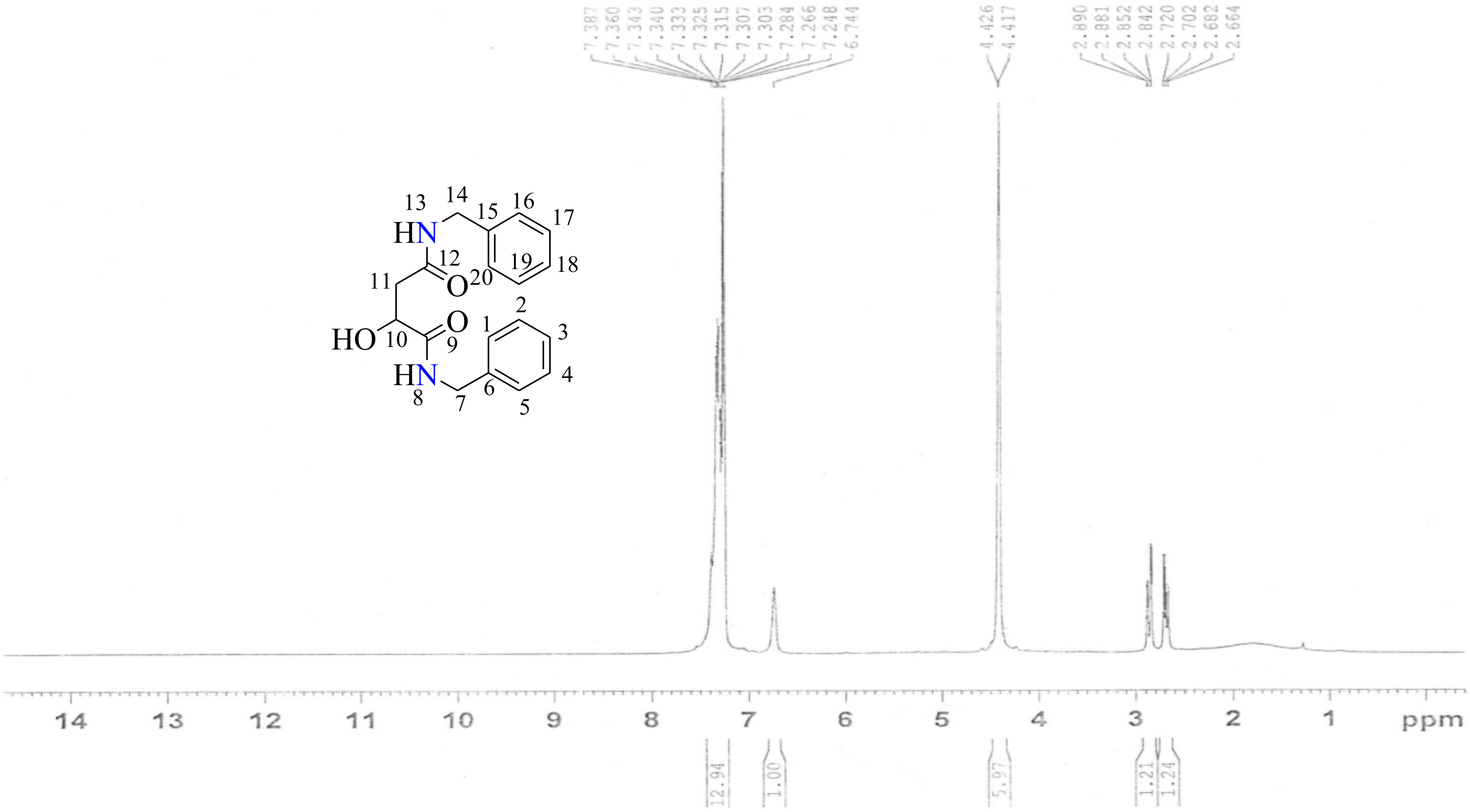


Fig. 3.9.5 (c): ^{1}H-NMR spectrum of diamide-5.

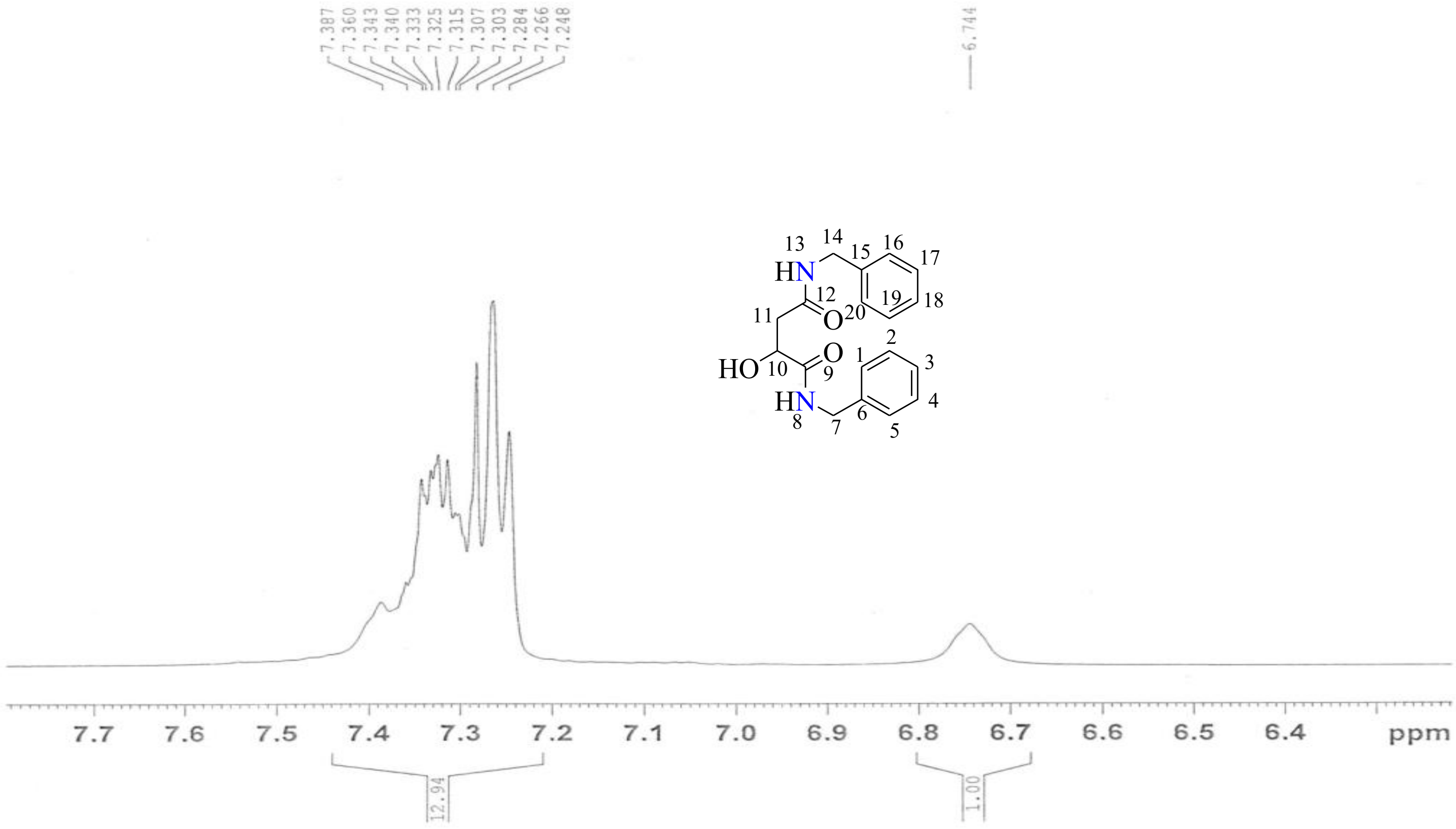


Fig. 3.9.5 (d): Extended ^{1}H-NMR spectrum of diamide-5.

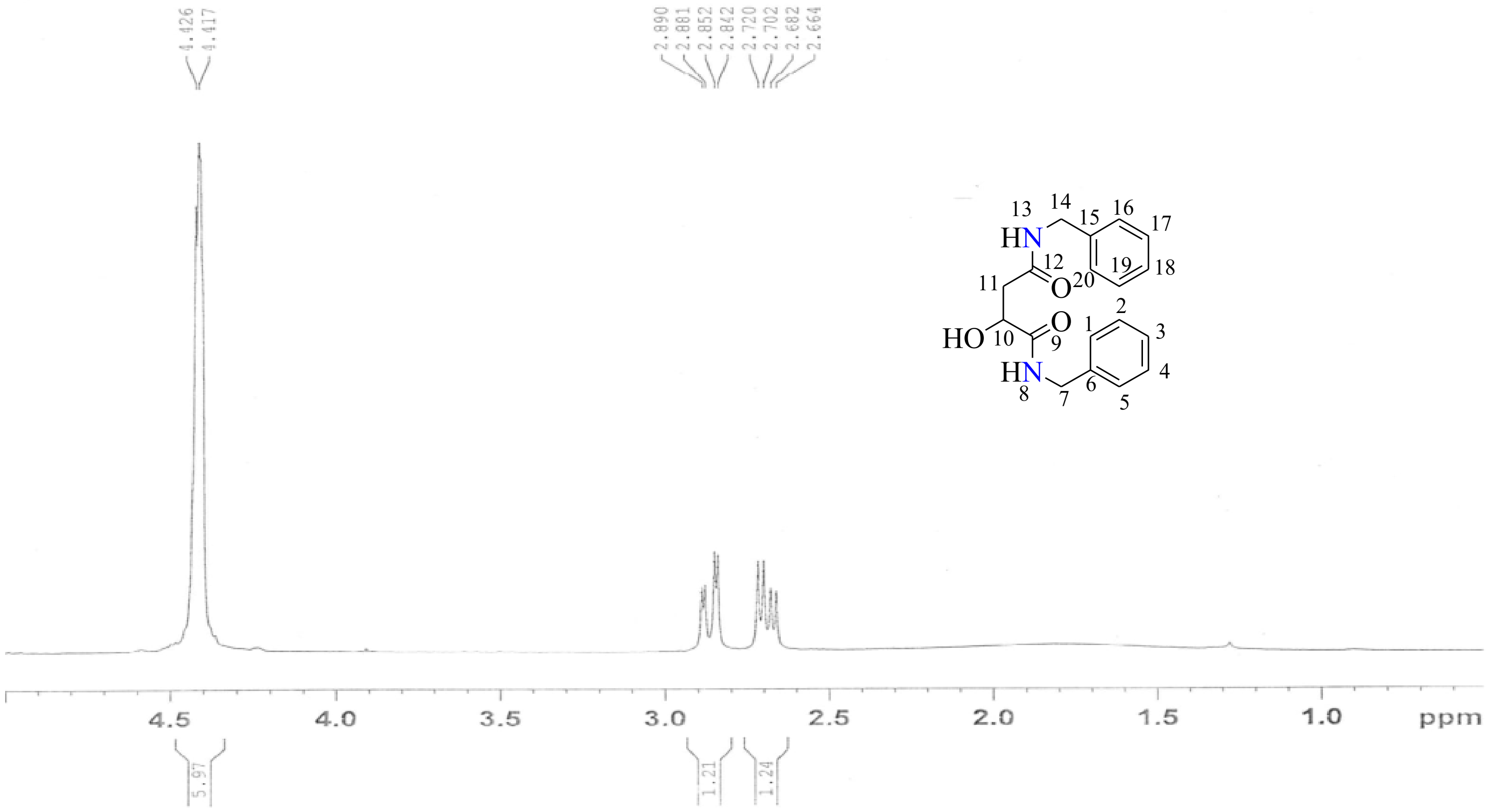
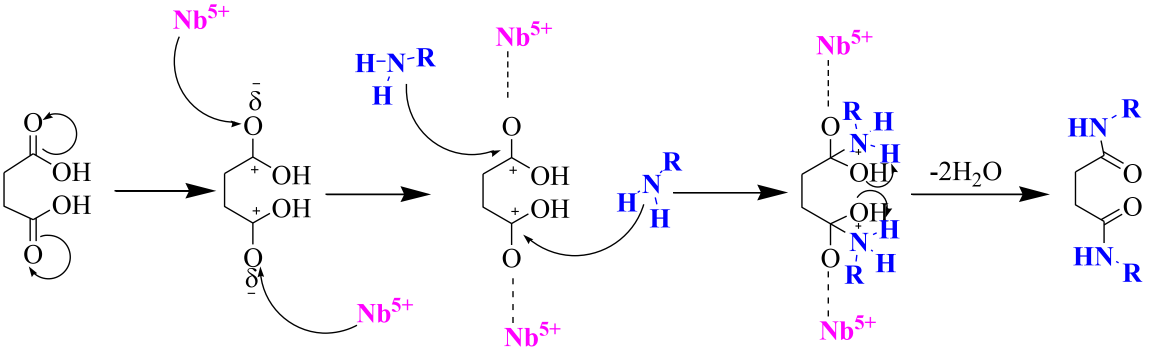


Fig. 3.9.5 (e): Extended ^{1}H-NMR spectrum of diamide-5.

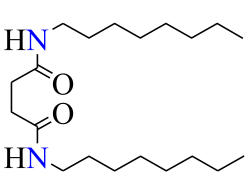
3.9.6. Possible reaction mechanism for diamide synthesis

Diamide synthesis from dicarboxylic acids with amines is a condensation reaction. In this reaction mechanism Nb^{5+} attack to carbonyl oxygen then amine (nucleophile) attack to carbonyl carbon and dehydration of two molecules of water and then form diamide. The possible mechanism is given below.

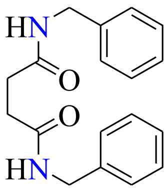


3.9.7. Summary

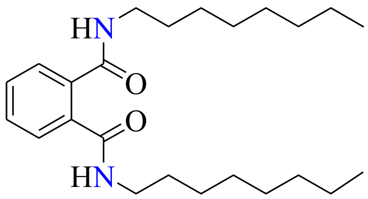
The summary of the synthesized diamide is given below.



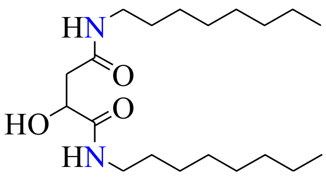
P-1



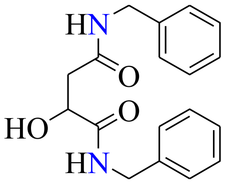
P-2



P-3



P-4



P-5

Chapter 4

Conclusions

4.1. Conclusions

In conclusion, it was shown that Nb_2O_5 acts as an effective heterogeneous catalyst for the synthesis of diamide from dicarboxylic acids and amines. Five different diamides were synthesized including *N*, *N*-dioctyl-butanediamide, *N*, *N*-dibenzyl-butanediamide, *N*, *N*-dioctyl-pthalamide, *N*, *N*-dioctyl-2-hydroxy-butanediamide and *N*, *N*-dibenzyl-2-hydroxy-butanediamde using Nb_2O_5. These synthesized diamide can be used in medicine, pesticide, agrochemical, polymer and synthetic chemistry.

Since there is no reported method for the synthesis of diamide in presence of heterogeneous Lewis acid catalyst. So, it is said that a novel, versatile and sustainable method for synthesis of diamide from dicarboxylic acids with amines using Nb_2O_5 as a base tolerant, reusable, inexpensive and commercially available heterogeneous Lewis acid catalyst were established. This atom economical and simple method will provide a practical and convenient route for diamide from readily available starting materials. Lewis acid catalysis of Nb_2O_5 even in the presence of strong base may be applicable to other acid-catalyzed reactions involving carbonyl compounds.

Herein, it can be concluded that the first general catalytic method of direct diamide synthesis from dicarboxylic acids with amines using Nb_2O_5 as a base tolerant heterogeneous Lewis acid catalyst.

4.2. Reference

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