Direct Amidation of Carboxylic Acids over $FeCl_3$ Catalyst

SRIMATHI M

(20PCH022)

Thesis Submitted to

Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore- 641 043.

In Partial Fulfillment of the Requirements for the Degree of

MASTER OF SCIENCE IN CHEMISTRY

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Signature of the

Supervisor

Signature of the

Head of the Department

ACKNOWLEDGEMENT

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It is with the choice of blessings and the divine grace of **LORD ALMIGHTY** that any human endeavour is achieved.

I record my sincere thanks to **Prof. S.P. Thyagarajan**, Chancellor, Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore, for providing the support to do my research work.

I would like to thank **Dr. V. Bharathi Harishankar**, Ph.D., FRSA, Vice Chancellor, Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore, for providing opportunity to develop and establish my skills.

I extend my thanks to **Dr. (Mrs.) S.Kowsalya**, M.Sc, M.Phil, Ph.D., Registrar, Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore, for providing the favourable infrastructure to do my research work.

I express my heartfelt thanks to **Dr. (Mrs.) G. Padmavathi**, M.Sc., M.Phil., Ph.D., Dean, School of Physical Sciences & Computational Sciences, Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore, for her excellent support, and guidance during the course of the investigation.

I record my deep sense of gratitude to **Dr. (Mrs.) R. Saratha**, M.Sc., M.Ed, M.Phil., Ph.D., Professor and Head, Department of Chemistry, Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore, for her encouragement and for providing all lab facilities at any time throughout my study.

I specially acknowledge my deep sense of gratitude and respect to my guide Dr. (Ms.) **V.Sharulatha**, M.Sc, M.Phil, Ph.D., NET, Assistant professor (SS), Department of Chemistry, Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore, for her meticulous care, eminent guidance, and enormous help and continuous encouragement throughout my project. I am grateful for her constant support for the successful completion of thesis work efficiently and effectively.

I would like to express my sincere thanks to all the Staff Members of the Department of Chemistry, Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore, for their help and support in the successful completion of this dissertation.

My special thanks to Ph. D research scholars **Abinaya. A, Kiruthika. S and Keerthana. L**, Department of Chemistry and my friends who have been with me in all my stages of work and supported me to do my work successfully.

A personal note and my special tribute to my beloved parents and my brother for their encouragement during my entire study.

SRIMATHI M

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LIST OF ABBREVIATIONS

DMSO	**Dimethyl Sulfoxide**
DMF	**Dimethyl Formamide**
FT-IR	**Fourier Transform Infrared**
H^1 NMR	**Proton Nuclear Magnetic Resonance**
TLC	**Thin Layer Chromatography**
TFA	**Trifluroacetate**
WEB	**Water Extract Of Banana**
TBHB	**tert-butyl hydroperoxide**
CAN	**Ceric Ammonium Nitrate**
DMAP	**N-N dimethylamino Pyridine**
EDC.HCl	**1-Ethyl-3-(3-dimethylaminopropyl) Carbodiimide**

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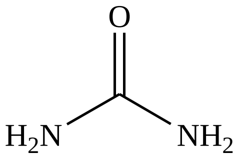
INTRODUCTION

1. INTRODUCTION

Organic synthesis has been continuously evolving to higher levels of sophistication and into new domains ever since its emergence in the early part of the nineteenth century. `The structure of the molecule and the ability to synthesize it in the laboratory constitute two of the most fundamental and influential discoveries of all time. The continuous evolution of structural chemistry and organic synthesis over the last two centuries has been rather dramatic, and so has their impact on science and society. Physical organic chemistry, a field that combines in many ways structure and synthesis, seeks to understand and correlate the structure of the molecule with its chemical reactivity and other physical and biological properties. **(K. C. Nicolaou, 2018)**

Organic synthesis benefited science and society enormously, both directly and indirectly through enabling technologies and game changing discoveries. Through organic synthesis, coal tar and petroleum were processed to useful products, besides medicines, such as fuels for energy, polymers and plastics, and other fine chemicals, a practice that continues to facilitate the energy sector and its technologies. The first laboratory synthesis of organic compound is "Urea" **(1)** from the inorganic compound by Friedrich Wohler in 1828. **(K. C. Nicolaou, 2018)**



Urea

(1)

And as we move into the future, organic synthesis is poised to contribute decisively, and in concert with other sciences and engineering, to the solution of global problems such as healthcare and nutrition, and to ensuring a sustainable and hospitable environment for humanity and life itself on our planet. While organic synthesis provided inspiration and impetus for the emergence of numerous disciplines, technologies and industries, it also benefited from them and instrumentations that had their fundamental origins from physics and mathematics. **(K. C. Nicolaou, 2018)**

1.1 CARBOXYLIC ACID:

Carboxylic acids are compounds with excellent chemical and physical properties, the most particular characteristics of this type of organic compounds, is their high solubility in polar solvents, as water, or alcohols, methanol, ethanol, etc. Carboxylic acids contain a carboxyl group (–COOH) and are oxoacids with the general formula R–COOH or Ar–COOH. Chemical structure contains a carbonyl function (-C=O) and an hydroxyl group (OH), these groups interact easily with polar compounds, forming bridges of H, obtaining high boiling points. The carbonyl group (C=O) is considered a one of the most functional groups involved in many important reactions.

This type of organic compounds can be obtained by different routes, some carboxylic acids, such as citric acid, lactic acid or fumaric acid are produced from by fermentation, most of these type of carboxylic acids are applied in the food industry. Historically, some carboxylic acids were produced by sugar fermentation. There are different synthesis reactions such as reactions of oxidation from alcohols in the presence of strong oxidants such as $KMnO_4$, oxidation of aromatic compounds among other routes. Derivatives of carboxylic acid, as alkyl halides, esters, and amides, present different and important application in diverse areas. In the case of the amides, it is obtained in the presence of an amine, may be primary and secondary, with a carboxylic acid, in this reaction also can be used a catalyst and heat to accelerate the reaction. Due to their chemical and physical characteristics, this type of organic compounds presents innumerable applications in the different areas, such as medicine, pharmacy, organometallic, polymer, nanotechnology, food, among others. The use of carboxylic acids in organic synthesis is a very wide area and the chemical transformations of this group to another have made it a very versatile functional group. **(Aide Saenz Galindo *et al.*,)**

1.2 AMIDE:

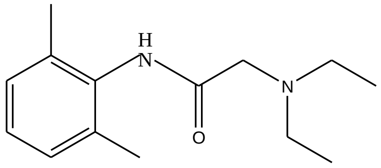
The amide functionality is one of the most fundamental chemical building blocks found in nature. Amide bonds are present in a vast array of useful molecules including numerous industrially important compounds, as well as a wide selection of bioactive natural products. **(Rachel M. Lanigan, 2013)**

Amide is a key functional group in organic chemistry for its widespread occurrence in peptide and non-peptide natural products, therapeutic small molecules, and new polymeric materials. **(Antonella Leggio *et al.*, 2017)** The synthesis of amide is of huge importance in organic, coordination, and medicinal chemistry. Improved and innovative methods for the synthesis of amides are in great demand both by chemical and pharmaceutical industry.**(Helena Lundberg *et al.*, 2012)**

The importance of the amide functional group emerges from their presence in many crucial compounds such as proteins, fabrics, fertilizers, insecticides, plastics, drugs, and in a vast number of synthetic structures. For this reason, it is very relevant to develop new methods for the efficient synthesis of amide. **(Danny C. Lenstra *et al.*,)**

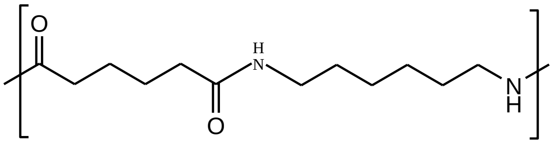
The -CO-NH- bond is one of the important functional groups found in various natural products, and it is also one of the high profile moieties in modern medicinal chemistry. Amide bond played a key role in a biological system, and comprehensive database analysis revealed that the carboxamide group appears in more than 25% of the known drugs. This percentage occurrence in many drugs may be expected since carboxamide bonds are stable, neutral, and have both hydrogen bond donor and acceptor properties. The amide functionality is a common feature in small or complex synthetic or natural molecules. It is ubiquitous in life as proteins play a crucial role in virtually all biological processes such as enzymatic catalysis, haemoglobin, immune protection, and mechanical support. **(A. Rosie Chhatwal *et al.*, 2020)**

Amide bonds constitute the skeleton of biologically important proteins, several drugs, including penicillin and paracetamol, and also widely used synthetic polymers, such as nylon. **(Md. Ayub Ali., 2016)** Polymers based on the amide linkage are of importance in a wide range of applications, from everyday materials such as Lindocaine (anesthetic)**(2)**, nylon**(3)**, Tebufenozide (insecticide)**(4)**, Aspartine (Sweetner)**(5)** to more advanced uses in drug delivery systems, adhesives and wound healing. In addition, the amide bond is commonly found as a key structural element in agrochemicals and in products from the fine chemicals industry. **(Helena Lundberg, 2015)**



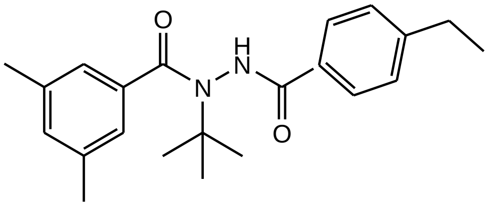
Lidocaine (anesthetic)

(2)



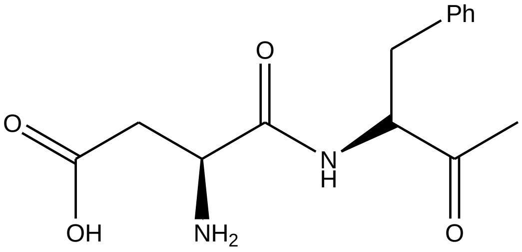
Nylon 6,6 (polymeric material)

(3)



Tebufenozide (insecticide)

(4)



Aspartine (Sweetner)

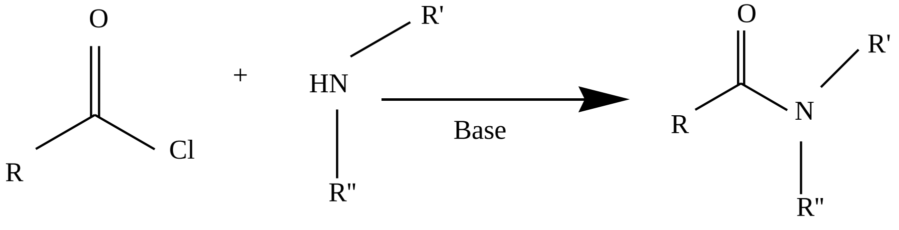
(5)

Amides contain a functional group which consists of a C=O (carbonyl) directly bound to nitrogen. 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. **(David Diaz Diaz *et al.*, 2006)**

Amide is the generic term for compounds derived from oxoacids by replacement of an acidic hydroxy group with an amino group or substituted amino group. Compounds containing up to three acyl groups bonded to a single nitrogen atom are included in the generic class. Primary, secondary, and tertiary amides contain one, two, and three acyl groups, respectively. Amides are classified based on the types of oxoacids from which they are derived (e.g., carboxylic acids become carboxamides, sulfonic acids become sulfonamides, etc.). The simplest carboxamides are primary amides containing an unsubstituted NH2 group.

1.3 SYNTHESIS OF AMIDE:

One of the most popular synthesis of amide bonds is the Schotten-Baumann reaction, first described in 1883 by Carl Schotten and Eugen Baumann. This reaction is the coupling of an acid chloride **(6)** and an amine **(7)** to produce an amide **(8)** and hydrochloric acid. **(Helena Lundberg, 2015)**



(6) **(7)** **(8)**

Conventionally, amides are prepared from carboxylic acids and amines via activated carboxylic acid derivatives such as carboxylic acid anhydrides or acyl chlorides or via activation with stoichiometric amount of a condensation agent for activation of carboxylic acid and water removal. The conventional methods suffer from low atom efficiency and production of byproducts. It is generally accepted that the catalytic synthesis of amides from readily available starting materials is the priority area for the pharmaceutical industry. **(David Diaz Diaz *et al.*,2006)**

$$\underset{\text{Acid}}{\text{R-COOH}} \xrightarrow{\text{SoCl}_2} \underset{\text{Acetyl chloride}}{\text{R-COCl}} \xrightarrow{\text{aq. NH}_3} \underset{\text{Amide}}{\text{R-CONH}_2}$$

Reaction time 6-16 hours

Conventional method of amide synthesis

Amides are most often prepared from carboxylic acids and amines, either via formation of more reactive carboxylic acid anhydrides or acyl chlorides, or via activation with coupling reagents. Most of the current synthetic methods for the formation of the amide bond are, however, limited to the use of stoichiometric amounts of reagents that activate carboxylic acids. The formation of the amide bond under catalytic conditions is considered as one of the grand challenges of modern organic chemistry. **(Md. Ayub Ali, 2016)**

Recent endeavors have demonstrated the promise that amides can be synthesized from various readily available starting materials, including the most preferred pair of carboxylic acids and amines. **(Md. Ayub Ali, 2016)** Formally, the amide bond is formed through the condensation of a carboxylic acid and an amine with the release of one equivalent of water. This reaction has been considered challenging due to the competing acid–base reaction, which occurs when the amine and the carboxylic acid are mixed. **(J.S. Yadav *et al.*, 2008)**

Although the amide bond can be formed from the corresponding ammonium carboxylate salt upon heating, this reaction has generally been considered to be of limited preparative value. Furthermore, the high activation barrier for the direct coupling of a carboxylic acid and an amine can only be overcome using forcing reaction conditions. **(J. S. yadav *et al.*,2008)**

1.4 IRON (III) CHLORIDE CATALYST:

Catalysis is a key technology, since approximately 80% of all chemical and pharmaceutical products on an industrial scale are made in presence of catalysts. During the last decades, manifold transition-metal catalysts especially based on precious metals such as palladium, rhodium, iridium, and ruthenium have been proven to be efficient for a large number of applications in organic synthesis. However, their high price as well as toxicity makes it desirable to search for more economical and environmentally benign protocol. A possible solution of this problem could be the increased use of catalysts based on first row transition metals, such as iron, copper, zinc, and manganese. Especially iron offers significant advantages compared with precious metals, since it is the second most abundant metal in the earth crust. The facile change of oxidation state and the distinct Lewis acid character, iron catalysts allow in principle a broad range of synthetic transformations, for example, addition reactions, substitution reactions, cycloaddition, hydrogenation, reduction, oxidation, coupling reactions, isomerizations, rearrangements, and polymerizations. **(Basavaprabhu *et al.,* 2015)**

Among various transition metal-complexes, non-toxic and inexpensive ferric chloride is a very water-soluble and strong oxidizing agent, which is obtained as dark-green, lustrous crystals by heating iron in chloride, and has found important applications in medicine where it has been used for a century as an alcoholic solution called tincture of iron. **(David Diaz Diaz *et al.,*2006)**

In recent years, Iron (III) chloride has emerged as a powerful Lewis acid catalyst and performs many useful organic transformations under mild reaction conditions. Moreover, iron salts are inexpensive, easy to handle and are environmentally friendly. **(J. S. Yadav *et al.,* 2008)** Iron (III) chloride has played an important role in the catalysis of the Friedel-Crafts reaction, which has been extensively studied in the past using various Lewis acid catalysts and protonic acids. Because of ready access to these reagents, mild reaction conditions, easy work-up, usually one-step conversion and excellent yields, iron (III) chloride has been considered to be a ecofriendly, simple, and mild catalyst to be taken into account in many synthetic problems. **(David Diaz Diaz *et al.,* 2006)**

In this study, the carboxylic acid undergoes amidation reaction with different substituted amines in the presence of $FeCl_3$ catalyst. The structure is characterized by FTIR spectrum and NMR spectroscopy.

1.5 OBJECTIVES

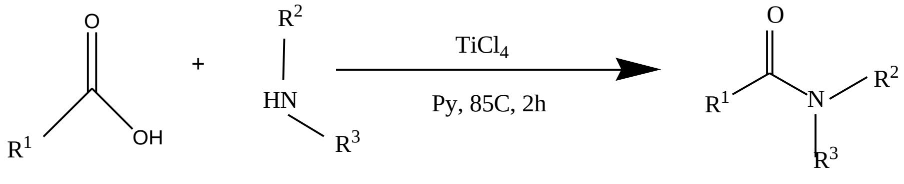
The amidation reaction of Phenylacetic acid with aniline in the presence of Ferric chloride ($FeCl_3$) catalyst and toluene yielded corresponding amide **Basavaprabhu *et al.*, in 2015.** But the structure was not confirmed by spectroscopic data. **In 2018, Leiling Deng *et al.*,** reported the reaction of Phenylacetic acid toward N-Substituted benzamides with copper(II) mediated catalyst yields corresponding primary and secondary amides. The reaction of amine with carboxylic acid in the presence of DMF and $FeCl_3$ catalyst yielded corresponding amide **(Basavaprabhu *et al.*, in 2015)** with the above mentioned views, the present work aims.

- ✓ To prepare 3-(3-(l2-azaneyl)-3-oxopropyl)-4-methylquinolin-2(1H)-one-1,3-dimethoxy-2-methylbenzene, 3-(3-(l2-azaneyl)-3-oxopropyl)-4-methylquinolin-2(1H)-one-o-tolyl-l1-sulfane-toluene, 3-(2-(l2-azaneyl)-2-oxoethyl)-4-phenylquinolin-2(1H)-one-toluene from Glutaric acid 2-amino acetophenone and Succinic acid 2-amino benzophenone.
- ✓ To carry out the reaction in the presence of $FeCl_3$ catalyst.
- ✓ To verify the presence of functional groups in the synthesized compound by FTIR.
- ✓ To predict the structure of the synthesized compound by H^1NMR technique.

REVIEW OF LITERATURE

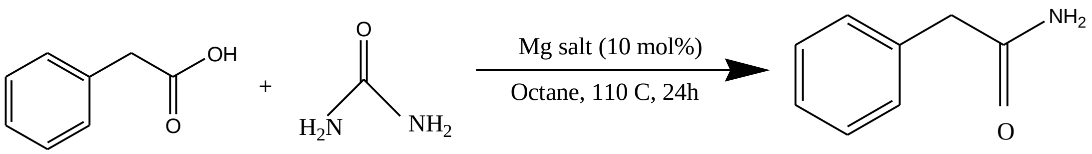
1. REVIEW OF LITERATURE

Antonella Leggio *et al.*, (2017) studied the formation of amides by one-pot condensation of carboxylic acids **(9)** and amines **(10)** mediated by $TiCl_4$. There are different lewis acid catalyst was used to synthesize amide from carboxylic acid. They are $TiCl_4$, $ZrCl_4$, $ZrCp_2Cl_2$ which gave more yields of amides **(11)**. In this study Titanium tetrachloride was used as a catalyst for the synthesis of secondary and tertiary amides from various carboxylic acid precursors. The condensation reaction of Benzoic acid was carried out in base or solvent of pyridine at 85℃ gives the product of N-Phenylbenzamide in 98% yield and high degree of purity. When both carboxylic acid and amines are sterically hindered, the reaction proceeds in low yields.



(9) (10) (11)

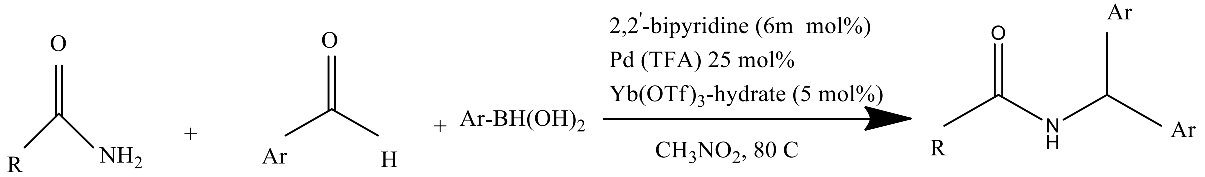
A.Rosie Chhatwal *et al.*, (2020) investigated the direct synthesis of amides from non-activated carboxylic acids using urea as nitrogen source and $Mg(NO_3)_2$ or imidazole as catalysts. This study involved the direct synthesis of primary and secondary amides from carboxylic acids using $Mg(NO_3)_2$ or imidazole as a low cost and readily available catalyst and urea **(13)** was used as a nitrogen source. Phenyl acetic acid **(12)** is converted into 2-Phenylacetamide **(14)** under Mg and Imidazole catalytic conditions. Therefore this conversion does not require the coupling or activating agents.



(12) (13) (14)

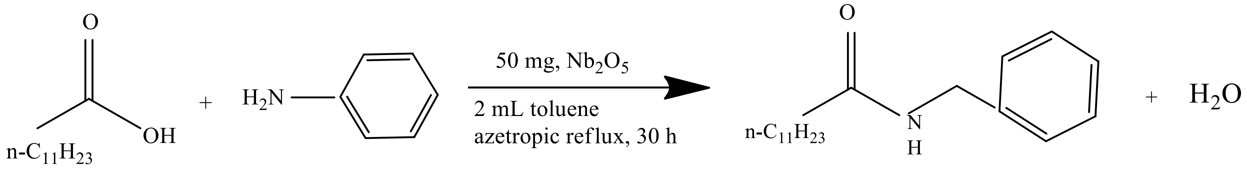
Tamara Beisel *et al.*, (2013) analysed a lewis acid Palladium (II) -Catalyzed Three-Component synthesis of α-Substituted amides. The Petasis or Borono-Mannich reaction is a three component reaction of an amine, an aldehyde, and a boronic acid allows the synthesis of various nitrogen containing molecules. A reaction between benzamine **(15)**, Benzaldehyde **(16)**

and phenyl boronic acid **(17)** is catalysed by lewis acid catalyst Pd(II) salts along with Yb(OTf)$_3$ gave highest and more reproducible result. When Yb(OTf)$_3$ is combined with Pd(TFA) and 2,2’Bipyridine the desired product yield is 86%. If any one of the compound is absent during the reaction, no product was formed. A dual catalyst system, consisting of a Lewis acid Yb(OTf)$_3$ and a palladium(II) salt, and the presence of water in the reaction are key to a successful transformation to get better yield of appropriate products.



(15) (16) (17)

Md. A. Ali *et al.,* Studied the Amidation of Carboxylic acids with amines by Nb_2O_5 as reusable lewis acid catalyst. The reaction of n-dodecanoic acid **(18)** with a less reactive amine (aniline) **(19)** in the presence of Nb_2O_5 catalyst showed highest yield. The catalytic amidation by a Nb_2O_5 was applicable to a wide range of carboxylic acids, amides with various functional groups, and the catalyst was used as a reusable catalyst. The comparison of the results of catalytic study and IR study of acetic acid adsorbed on the catalyst suggested that the activation of carbonyl group of carboxylic acid by the lewis sites on Nb_2O_5 is responsible for high activity. The direct formation of amides from amines and carboxylic acid without catalyst occurs in non-polar solvents under azeotropic reflux conditions. In thermal reaction without catalyst, the yield of amide is 1%. Whereas Nb_2O_5 shows 99% yield of amide. The higher catalytic efficiency of Nb_2O_5 can be due to high water-tolerance and more effective lewis acid activation of C=O bond. The amidation of different carboxylic acid using Nb_2O_5 were discussed.

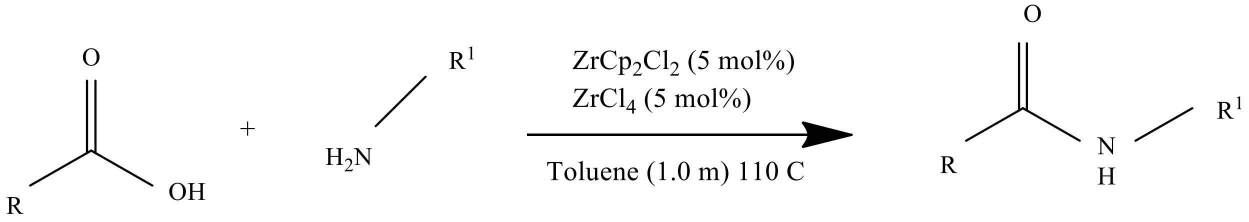


(18) (19)

C. Liana Allen *et al.,* (2011) studied the direct amide **(22)** formation from unactivated carboxylic acids **(20)** and amines **(21)**. The direct amide formation was simple in non-polar solvents and tried the coupling of 3-phenylpropanoic acid with 4-methylbenzamine in variety of solvents. Toluene acted as an excellent solvent for the uncatalyzed direct formation of amides.

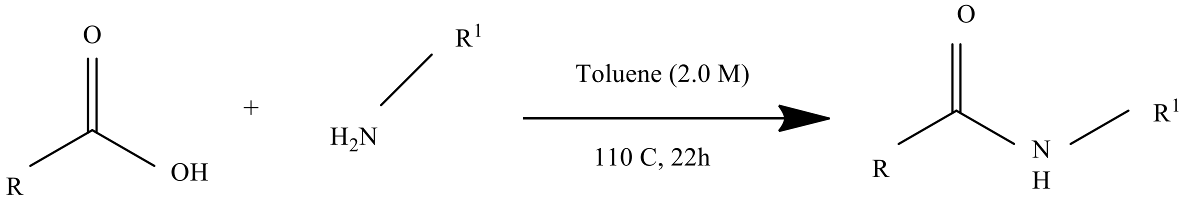
The conversion of amide from acid without catalyst proceeds to 20% conversion. The best result was achieved when using $ZrCl_4$ catalyst which gave 83% conversion after 4 hour. The catalyst $ZrCp_2Cl_2$ accelerates the reaction to 83% conversion into secondary amides. The thermal agitation of carboxylic acids with amines occurs at 110 °C in toluene in wide range of substrates. Some simple Lewis acid catalysed reactions and two zirconium catalysts were particularly effective for amide synthesis.

Direct catalysed formation of amides



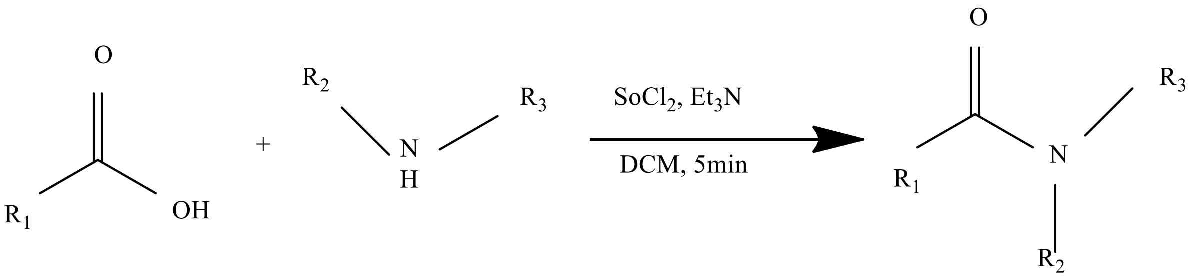
(20) (21) (22)

Direct uncatalyzed formation of amides



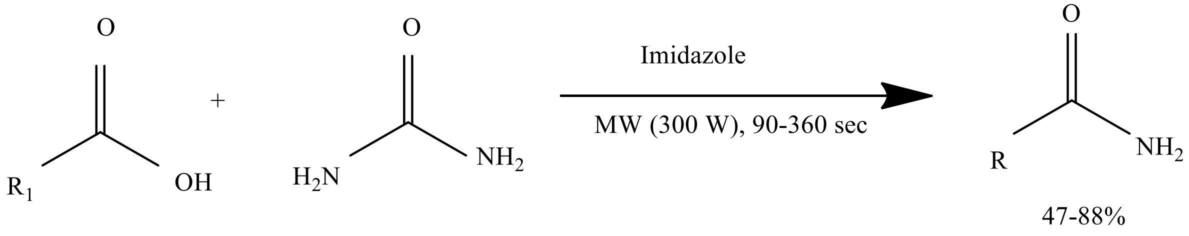
(20) (21) (22)

A. Leggio *et al.*, (2013) studied the one pot synthesis of amides from carboxylic acids activated using thionyl chloride. The secondary and tertiary amides were synthesized from carboxylic acid and amines by using $SOCl_2$. The excellent yield of amide was obtained when sterically hindered amines were used as starting materials. The amidation of N-protected α-amino acids with secondary amine gives good yields. The Thionyl chloride was used as a chlorinating agent in the formation of acyl chlorides and also functions as a coupling agent by activating *in situ* the carboxylic function of acid. Benzoic acid **(23)** was reacted with 1mmol of diethylamine **(24)** and 3 mmol of triethylamine in dichloromethane and then 1 mmol of $SOCl_2$ was added. The compound diethylbenzamide **(25)** was obtained in 86% yield. The molecular structure was determined by ^1H and ^{13}C NMR spectroscopy and GC/MS analysis. The additional experiment was performed to investigate the progress of reaction in the absence of tertiary amine. The product N,N-diethylbenzamide was recovered with 31% yield. The result demonstrates that the presence of tertiary amine is essential to obtain amide in high yields. This approach successfully extended to α aminoacids bearing acid sensitive groups and to the synthesis of dipeptide system, these results prove the applicative validity of the developed procedure also in peptide synthesis. This reaction can be applied for large-scale synthesis of amides of semi-industrial intrest.



(23) (24) (25)

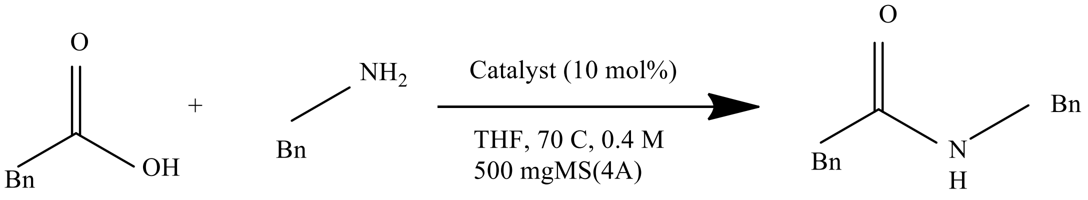
Ali Khalafi-Nezhad *et al.,* (2003) analyzed the Direct preparation of primary amides from carboxylic acids and urea using imidazole under microwave irradiation. Various aliphatic and aromatic amides were prepared by direct amidation method of good yields. The procedure for the synthesis of primary amides **(28)** by reaction of carboxylic acid **(26)** and urea **(27)** in the presence of imidazole under microwave irradiation was described. In this article, instead of imidazole they used other bases such as 4-dimethylaminopyridine, tri ethyl amine and 1,8-diazobicyclo[5,4,0]undec-7-en. But none of the bases acted as well as imidazole. The different substituted carboxylic acid reacts with urea in the presence of imidazole gives different amides with good yield. The aromatic carboxylic acids are less reactive than aliphatic acids. In the case of aromatic carboxylic acid, the presence of electron withdrawing groups accelerates the reaction rate and increases the yield. It concludes that the microwave assisted procedure provides efficient and easy methodology for the preparation of preparation of primary amides with good yields under solvent free conditions.



R- alkyl, aryl

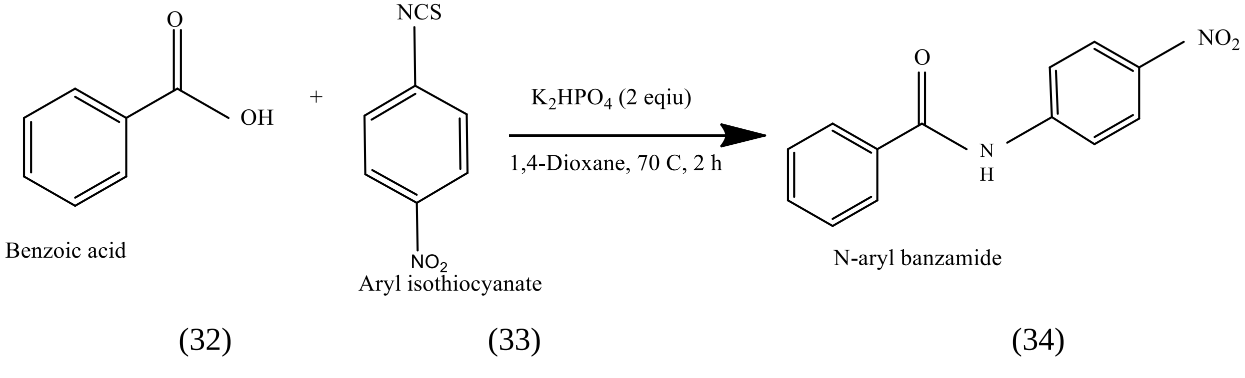
(26) (27) (28)

Helena Lundberg *et al.,* (2012) analyzed Titanium (IV) Isopropoxide as an efficient catalyst for direct amidation of Non-activated carboxylic acids. Titanium isopropoxide is an inexpensive and widely used chemical compound. The percentage of yield is noted when phenyl acetic acid **(29)** reacted with Benzamine **(30)** with different lewis acid catalyst was tabulated. The yield of secondary amide **(31)** and tertiary amide is good to excellent with a catalyst Titanium Isopropoxide. For the tertiary amide formation, the high temperature and more catalyst is required to get good yield. It was concluded that transition-metal catalyst are efficient catalyst for the direct amidation of non-activated carboxylic acid with amines.



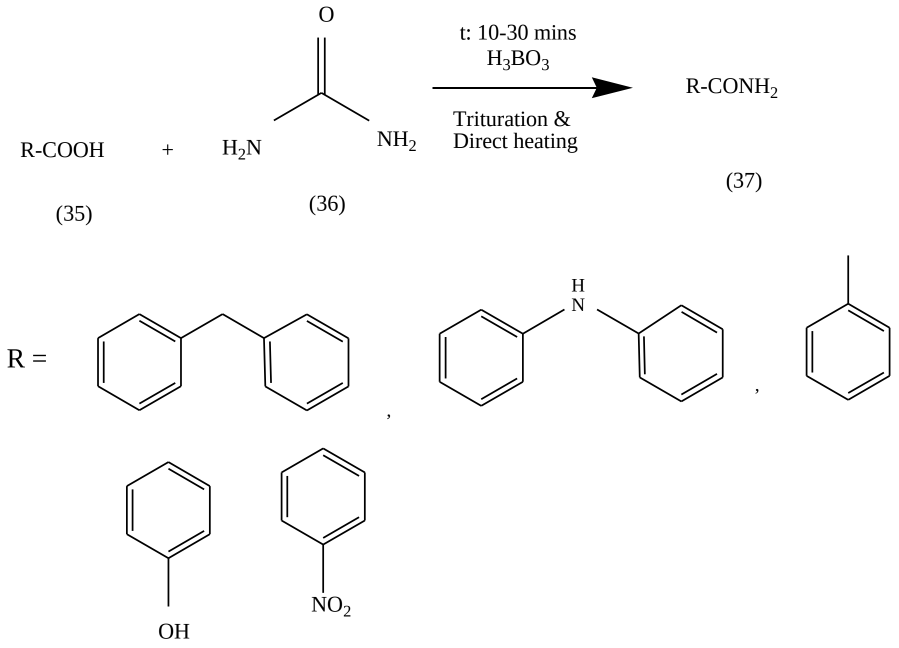
(29) (30) (31)

Tallapally Swamy *et al.,* (2017) studied the efficient method for the synthesis of Benzamides from Benzoic acids and Aryl Isothiocyanates using K_2HPO_4. It was an efficient and convenient cross-coupling method for the synthesis of N-aryl benzamides **(34)** from benzoic acids **(32)** and aryl isothiocyanates. **(33)** K_2HPO_4 was used as an efficient reagent for the synthesis of N-aryl benzaamides. When benzoic acid was treated with 4-nitrophenyl isothiocyanate in the presence of K_2HPO_4 at ambient temperature over 2hr gave corresponding amide in 82% yield. The presence of electron donating groups (-Me, -OMe), electron releasing groups and halogen on the aromatic ring resulted in good yields. This reaction proceeds through C-N bond formation.

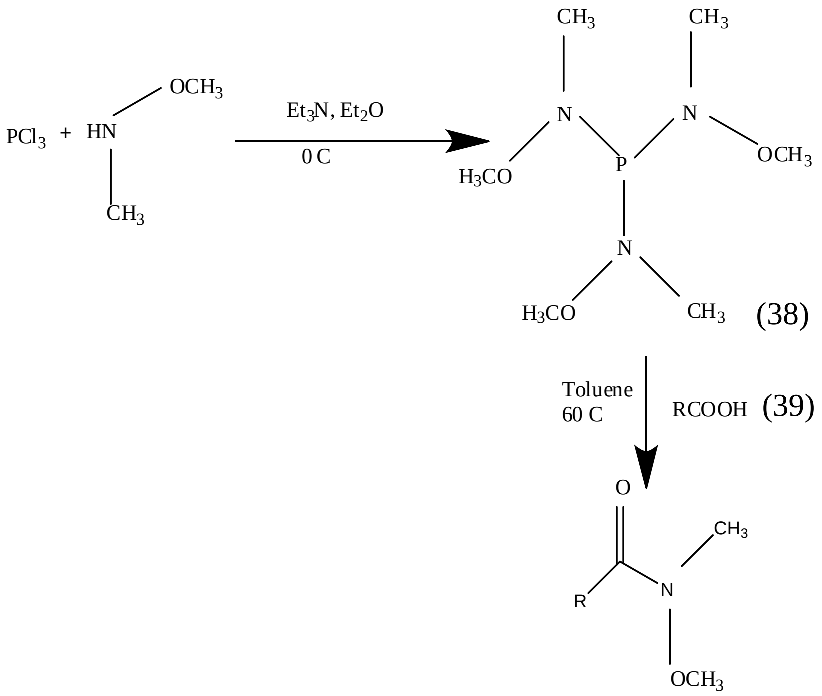


(32) (33) (34)

Chiragkumar J Gohil *et al.,* (2021) studied the Solvent-Free synthesis of amide: A Novel technique of green chemistry. The conventional method of synthesis of amide involves the reaction of carboxylic acid and amines and also involves the generation of hazardous chemicals and wastes. It was overcome by switching into green chemistry methods by reaction between carboxylic acid and urea. Boric acid was used as a catalyst. Different substituted amides **(37)** were synthesized by the reaction of solvent free, different carboxylic acid **(35)** with urea **(36)** and boric acid catalyst. The yield of corresponding product is noted. The presence of hydroxyl group on substituted carboxylic acid lowers the yield. The presence of nitro group on the aromatic ring increases the rate of reaction as well as yield.

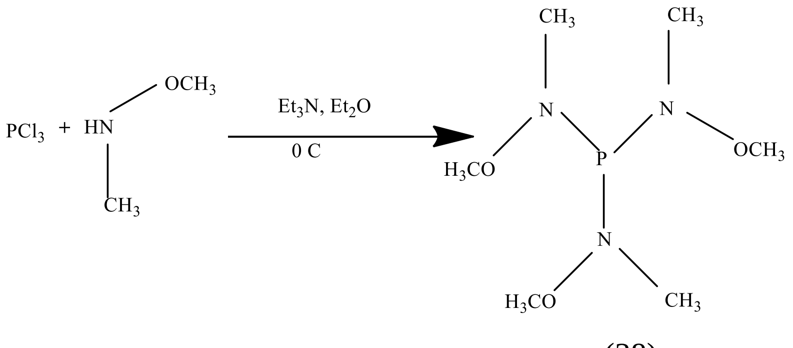


Teng Niu *et al.,*(2009) studied about powerful reagent for synthesis of Weinreb amides directly from carboxylic acids. Weinreb amide is also known as N-methoxy-N-methylamides **(40)**. The conversion of acid to Weinreb amide require powerful reagent $P[NCH_3(OCH_3)_3]$. When $P[NCH_3(OCH_3)_3]$ **(38)** was heated with aromatic and aliphatic acids **(39)** in toluene yields corresponding Weinreb amides with 90% yield. When the carboxylic acid is sterically hindered it gives corresponding amides in excellent yields. Benzoic acid and $P[NCH_3(OCH_3)_3]$ were heated at 80℃ for 1 hour in toluene. Similarly the reaction was carried in different solvent like CH_2Cl_2 or Et_2O, but yield was lower than that of toluene.



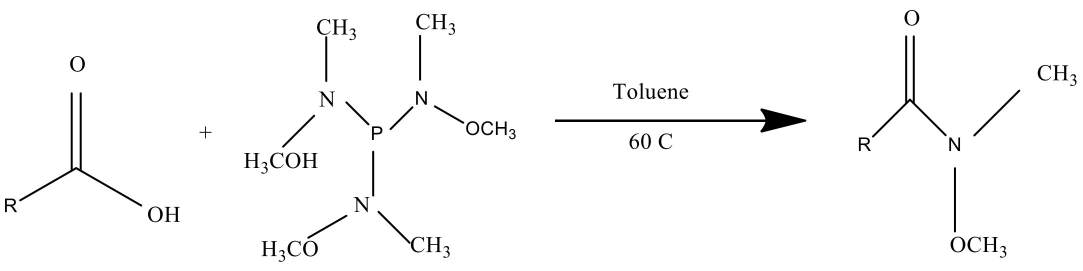
(38) (39) (40)

Synthesis of Catalyst P[NCH$_3$(OCH$_3$)]$_3$



(38)

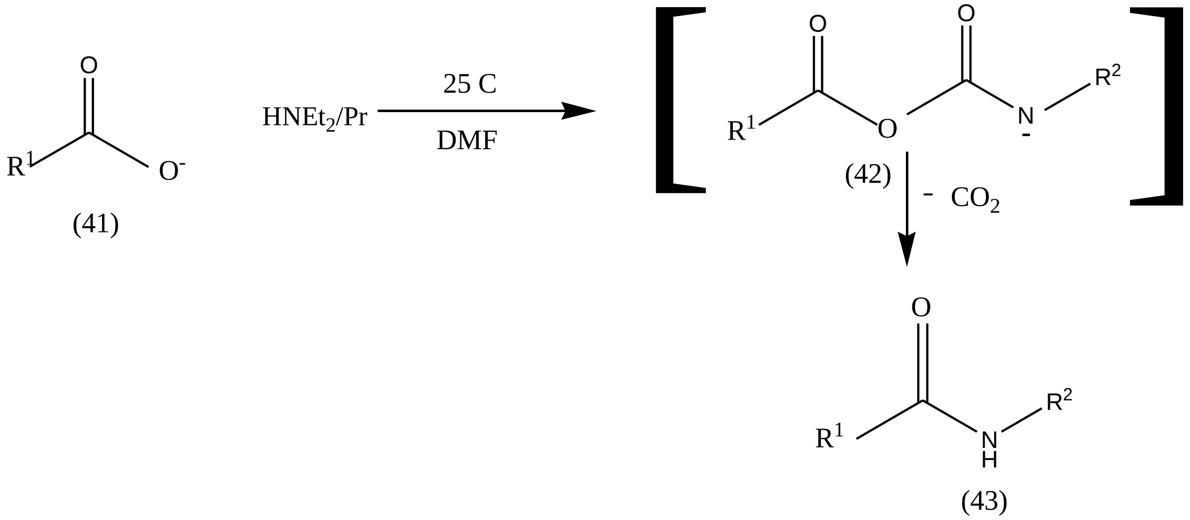
Synthesis of Weinreb amides from P[NCH$_3$(OCH$_3$)]$_3$ and Carboxylic acid



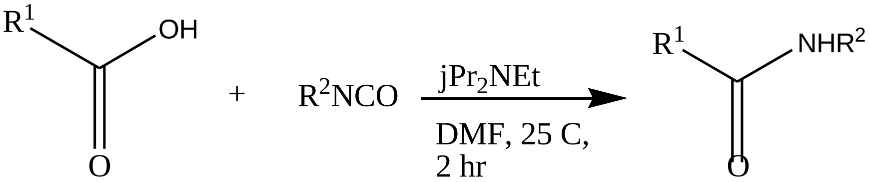
(39) (38) (40)

Jigar N. Soni *et al.*,(2014) studied the synthesis and antimicrobial; evaluation of amide derivatives of benzodifuran-2-carboxylic acid. The amide derivatives of benzodifuran-2-carboxylic acid were synthesized from resorcinol. 7-hydroxy-4-methylcoumarin on reaction with chloroacetone in anhydrous K_2CO_3 and dry acetone gave ether derivative of 7-hydroxy-4-methylcoumarin which on reaction with N-bromosuccinimide in chloroform gave corresponding 3-bromo derivative. Bromo derivative is cyclized with 10% ethanolic KOH resulted in benzodifuran-2-carboxylic acid. This acid was converted into acid chloride using oxalyl chloride and then reacted with different amines in the presence base resulted in amide derivatives of benzodifuran-2-carboxylic acid. The synthesized compounds were subjected to screen antimicrobial activity against gram positive, gram negative bacteria and fungal pathogens. The presence of electron withdrawing group at para position of amine showed moderate activity against gram positive bacteria *B. subtilis* while the presence of electron releasing group showed moderate activity against *S. aureus.* The synthesized compounds showed higher MIC values against gram negative bacteria *P. aeruginosa* and fungus *C. albicans.*

Kaname Sasaki *et al.*,(2011) investigated facile amide bond formation from carboxylic acids and isocyanates. Carboxylic acid in the form of their salts condenses with aryl isocyanates at room temperature with loss of carbondioxide to give corresponding amides in good yield. The condensation of carboxylate salts **(41)** with aryl **(42)** and other electron-deficient isocyanates at room temperature to give corresponding amides **(43)** and carbon dioxide is operationally simple, effective and atom-economical protocol.



Amide bond formation from carboxylate salts and isocyanates



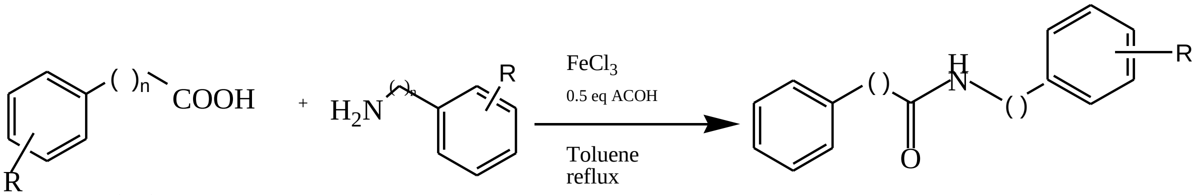
Kantharaju Kamanna *et al.*,(2020) studied microwave-assisted one-pot synthesis of amide bond using WEB. In this study it was demonstrated that simple and eco-friendly amide bond formation using carboxylic acid and primary amines through *in situ* generation of O-acylurea. Instead of traditional method enzymatic catalysis was investigated for amide bond formation under mild biochemical method. The carboxylic acid react with organic amine/amino acid ester in the presence of EDC.HCl, WEB and ethylene glycol in a microwave radiation for about 3-4 min at 300 W power it yields corresponding amide which is recrystallized with ethanol.

Vjekoslav Strukil *et al.*,(2012) studied one-pot mechanosynthesis of aromatic amides and dipeptides from carboxylic acids and amines. Environmentally friendly one-pot synthesis of amides, bis-amides and dipeptides by mechnochemical carbodimide-mediated coupling of carboxylic acid and amines was described with high reaction yields and simple aqueous work-up for the clean and fast preparation of variety of compounds containing amide bonds. The condensation of benzoic acid with *P*-anisidine yield N-(4-methoxyphenyl)-benzamide.

Chen Wang *et al.*,(2013) investigated mechanism of arylboronic acid-catalyzed amidation reaction between carboxylic acid and amines. Arylboronic acid was found to be efficient catalyst for the amidation of carboxylic acid and amines. It was found that formation of acyloxyboronic acid intermediates from carboxylic acid and the arylboronic acid was kinetically possible but thermodynamically unfavorable. The formation C-N bond formation between acyloxyboronic intermediates and amine can readily results in amide product. The mechanism of catalytic process was investigated by theoretical calculations. The rate determining step of the reaction is the cleavage of C-O bond of tetra-coordinate acyl boronate intermediate. Acetic acid reacted with methylamine in the presence of phenylboronic acid gives corresponding amine. When 2-phenylacetic acid reacts with benzylamine in the presence of 20% phenylboronic acid catalyst yields corresponding amide. The above mentioned reaction proceeds in two steps:

formation of acyloxyboronic acid intermediate and formation amide bond from the acyloxyboronic acid and amine.

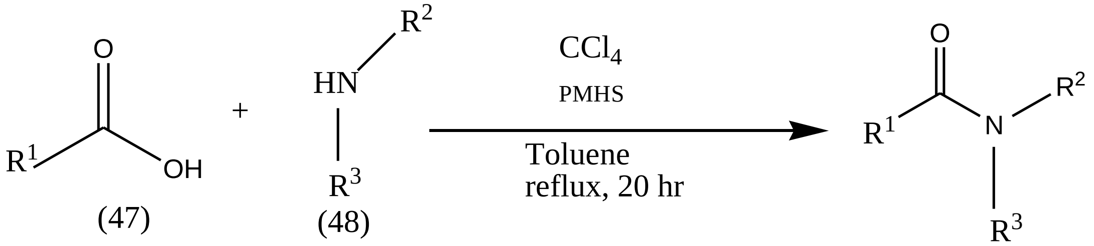
Basavaprabhu *et al.*,(2015) studied a simple and greener approach for the amide bond formation employing $FeCl_3$ as catalyst. In this study, it was described that the catalytic use of $FeCl_3$ in the presence of glacial acetic acid for the direct amidation of acid with amine in toluene. This reaction results in water soluble by-products so it makes easy to isolate the desired product. To a solution of Phenylacetic acid **(44)** in toluene add acetic acid and Ferric chloride catalyst which is stirred at 50℃ for 10-15 min. Then aniline **(45)** in toluene was added to the reaction mixture and was refluxed at 70-75℃ till the reaction got complete which is monitored by TLC. Finally, this reaction results in phenylacetamide. **(46)**



(44) (45) (46)

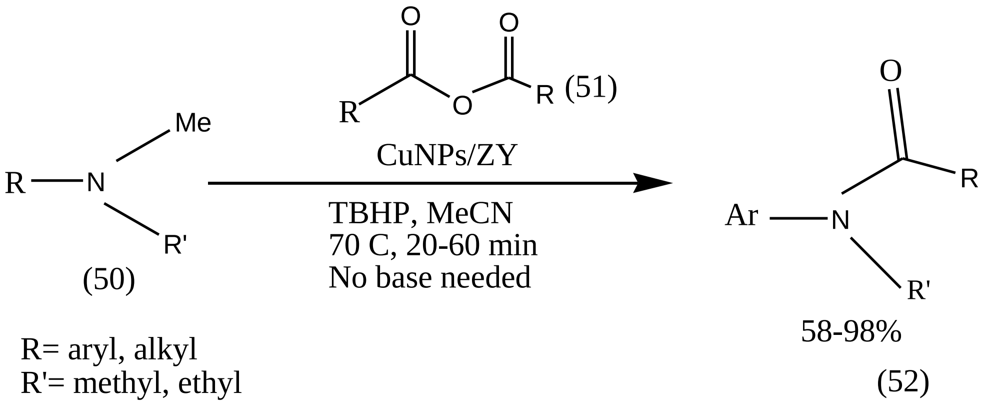
Daan F. J. Hamstra *et al.*,(2013) investigated poly(methylhydrosiloxane) as a green reducing agent in organophosphorus-catalysed amide bond formation. Poly(methoxyhydrosiloxane), a waste product of the silicon industry was used as an inexpensive and green reducing agent for *in situ* reduction of Phosphine oxide to phosphine. This method paves a way for the synthesis of wide range of secondary and tertiary amines in excellent yields. P-nitrobenzoic acid **(47)** reacted with benzylamine **(48)** in the presence of Ph_3P, CCl_4, Poly(methylhyroxysiloxane) and bis(p-nitrophenyl)phosphate at 110℃ in toluene yields 48% of N-benzy-p-nirobenzamide. **(49)**

Organophosphorus catalyzed reactions



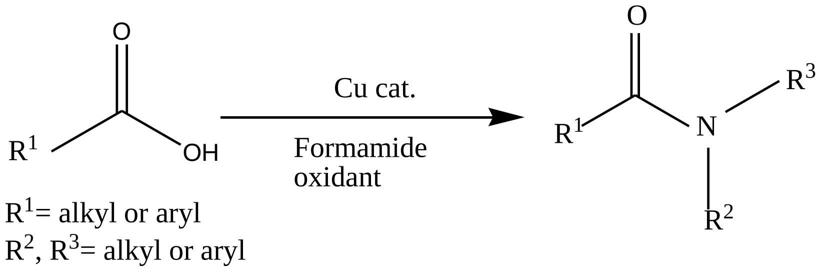
(47) (48) (49)

Yanina Mogile *et al.*, investigated amide bond formation catalyzed by recyclable copper nanoparticles supported on zeolite Y under mild conditions. The synthesis of amides from tertiary amines and anhydrides was tested by catalyst like copper nanoparticles in the presence of tert-butyl hydroperoxide as an oxidant. Copper nanoparticles on zeolite Y was found to be most efficient catalyst for the synthesis of amides when acetonitrile was a solvent under ligand- and base-free conditions in air. The products were obtained in good yield within a short reaction time. The copper nanoparticles on zeolite Y system exhibited catalytic activity than some commercially available copper and iron sources. N, N-Dimethylaniline **(50)** and acetic anhydride **(51)** undergo amidation reaction in the presence of copper nanoparticles on zeolite Y yields N-methyl-N-phenylacetamide **(52)** and minor amount of formyl amide.

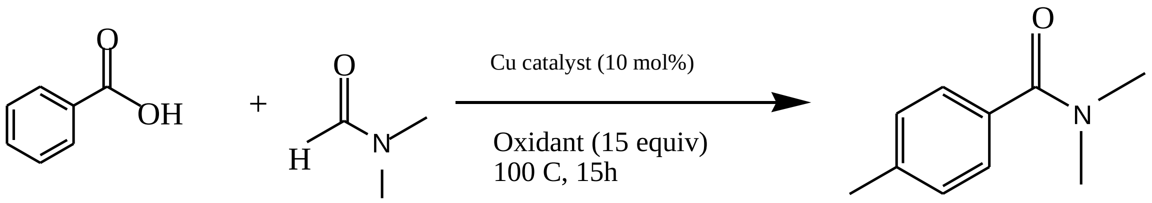


P. Santhosh kumar *et al.*,(2013) investigated copper-catalyzed oxidative coupling of carboxylic acids with N,N-Dialkylformamides: An approach to the synthesis of amides. Carboxylic acid **(53)** reacts with $Cu(ClO_4)_2.6H_2O$ and N,N-dialkylformamide **(54)** results in corresponding amide **(55)**. In this study, initially p-methylbenzoic acid and an excess amount of DMF was reacted by using $Cu(OAc)_2.H_2O$ as the catalyst and TBHP as a oxidant at 100℃ results in 58% of product. To get more yield further optimizations were done. The catalyst $Cu(ClO_4)_2.6H_2O$ results in higher yield of product.

Different approaches to the formation of amides



Optimization of reaction conditions

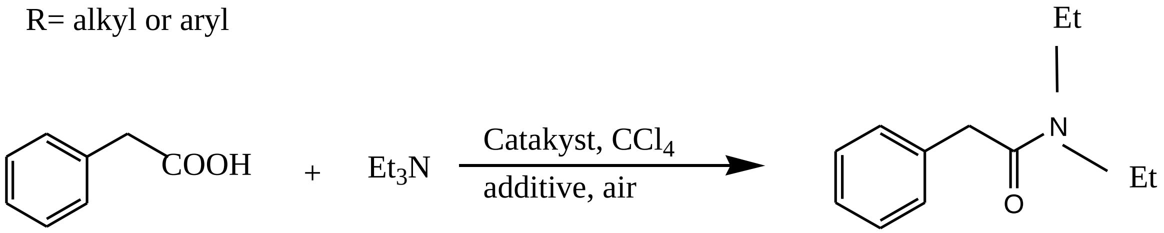


(53) (54) (55)

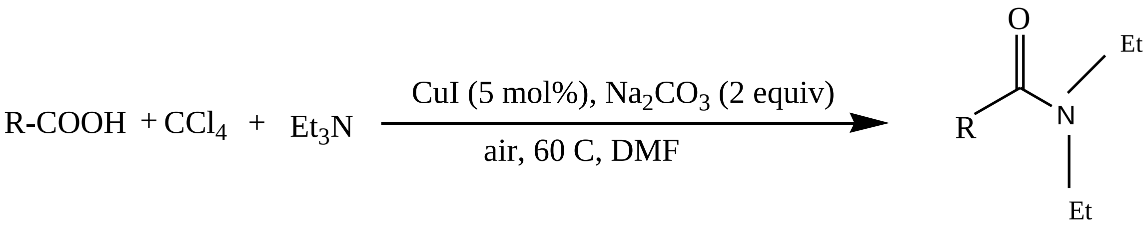
Biquan Xiong *et al.*,(2014) studied the direct amidation of carboxylic acids with tertiary amines: Amide formation over copper catalysts through C-N cleavage. In this study it was discussed that amidation of carboxylic acids with tertiary amines through C-N bond cleavage using copper catalyst. This reaction resulted in moderate to good yields. The reaction of phenylacetic acid **(56)** and triethylamine **(57)** using CuI as the catalyst yields 55% of corresponding amide. **(58)** When additives like K_2CO_3 and Na_2CO_3 was added to the reaction mixture leads to the increase in product yield. The different derivatives of amides were synthesized by reacting with different substrates of acid and amine.

$$\text{R-COOH} + \text{R}^3\text{-NR}^1\text{R}^2 \longrightarrow \text{RCO-NR}^1\text{R}^2$$

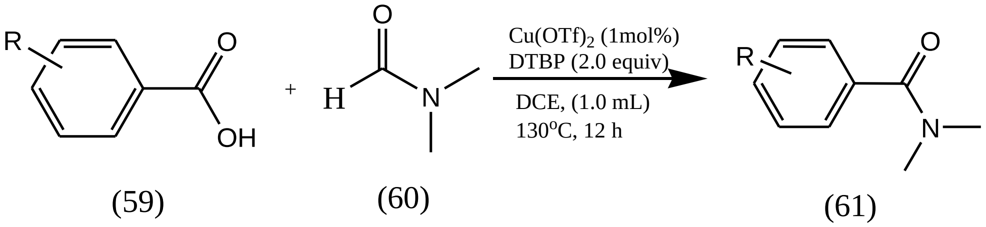
R= alkyl or aryl



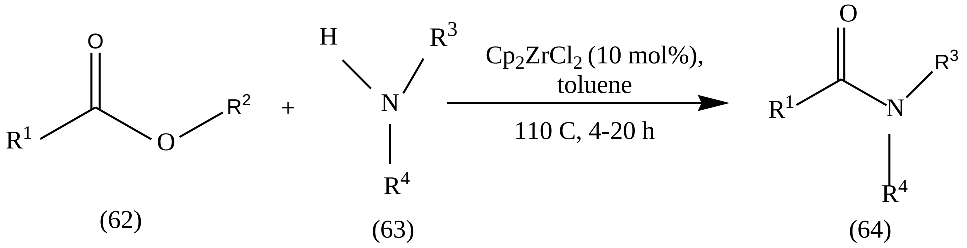
(56) (57) (58)



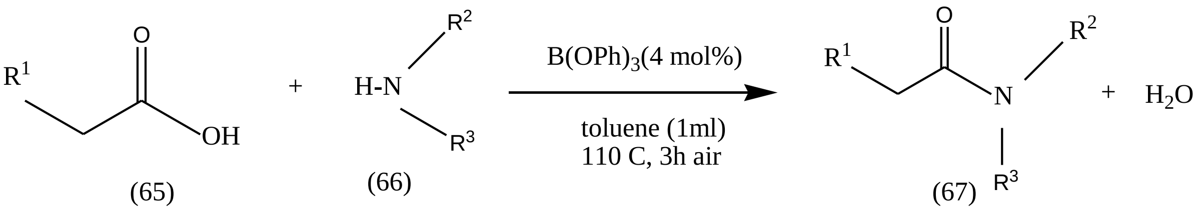
Hong-Qiang Liu *et al.*,(2014) investigated copper-catalyzed amide bond formation from formamides and carboxylic acids. Benzoic acid **(59)** reacts with formamide **(60)** in the presence of $Cu(OTf)_2$ yields corresponding amides. **(61)** Amidation of different formamides yields corresponding amide product. Different copper catalyst like CuI and $Cu(OTf)_2$ were involved in the reaction. The catalyst $Cu(OTf)_2$ results in better yield. This reaction shows that the presence of low amount of catalyst and reactant results in better yields.



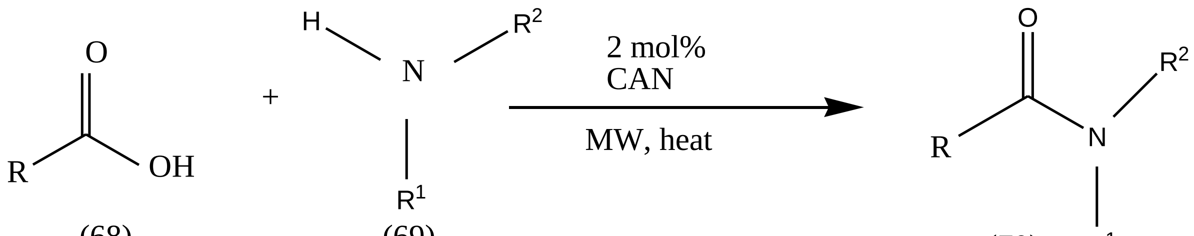
Danny C. Lenstra *et al.*,(2015) studied Zirconium-catalyzed direct amide bond formation between carboxylic esters and amines. This study involves the reaction of unactivated carboxylic esters **(62)** and amines **(63)** in the presence of 10 mol% of zirconocene dichloride (Cp_2ZrCl_2) in toluene at 110℃ results in corresponding amides **(64)** in very good to excellent yields.



Seema A. Ghorpade *et al.*,(2018) investigated Triphenyl borate catalyzed synthesis of amides from carboxylic acids and amines. The catalytic condensation of carboxylic acids **(65)** and amines **(66)** in the presence of triphenyl borate results amide **(67)** upto 92% yield. If the reaction proceeds in the absence of catalyst the yield is 9% which concludes that thermal amidation reaction is slower than catalytic amidation reaction. If sterically hindered amide involved in a reaction results in lower yield.



Adam P. Zarecki *et al.*,(2020) investigated Microwave-assisted catalytic method for a green synthesis of amides directly from amines and carboxylic acid. In this study, carboxylic acid **(68)** reacts with amines **(69)** under solvent-free conditions using very minute quantity of cerium ammonium nitrate (CAN) catalyst yields amide **(70).** This reaction was carried out in microwave reactor to obtain product fast and effective manner. This method results in cheap, high-yielding and green method for the direct amidation of carboxylic acids with different amines.



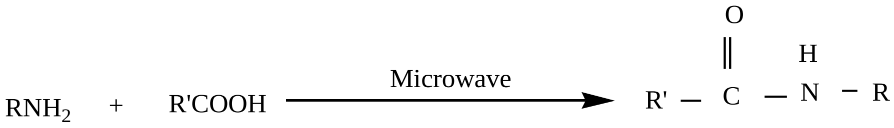
(68) (69) (70)

CAN- Ceric Ammonium Nitrate

Zhihui Wang *et al.*,(2018) studied direct formation of amides from carboxylic acids and amines catalyzed by Niobium (V) Oxalate Hydrate. This study explains that the formation of amides from carboxylic acid and amines was catalyzed by Niobium (V) oxalate hydrate. This reaction requires low catalyst loading of 1% in a ratio of 1:1 of acids and amines with the water removal through azeotropic distillation of toluene/water mixtures, which showed a good atom economic efficiency.

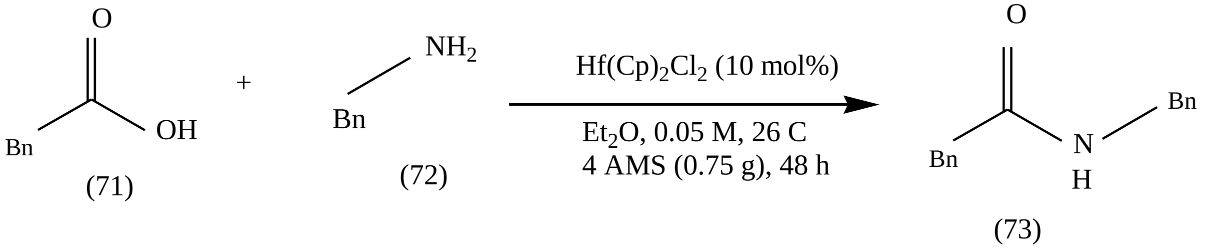
M. C. de Zoete *et al.*,(1996) investigated a new enzymatic one-pot procedure for the synthesis of carboxylic amides from carboxylic acids. This study involves the synthesis of amides from acids through *in situ* formation of the ester and subsequent ammoniolysis. Octanamide was synthesized from octanoic acid via butyl octanoate. The product octanamide was isolated in 93% yield. The procedure was given for the synthesis of compounds from octanoic acid.

Xiao-Jian Wang *et al.*,(2008) studied Microwave-Assisted synthesis of amide under solvent-free conditions. This study describes that the efficient and environmentally friendly synthetic method for the synthesis of primary amides under microwave radiation without any catalytic agents. The reaction took place within 8-12 min, which was shorter than traditional synthetic methods with good yields. Benzylamine and acetic acid were reacted in a microwave chamber, and an acylated compound was obtained. The yield was obtained as more than 90%.



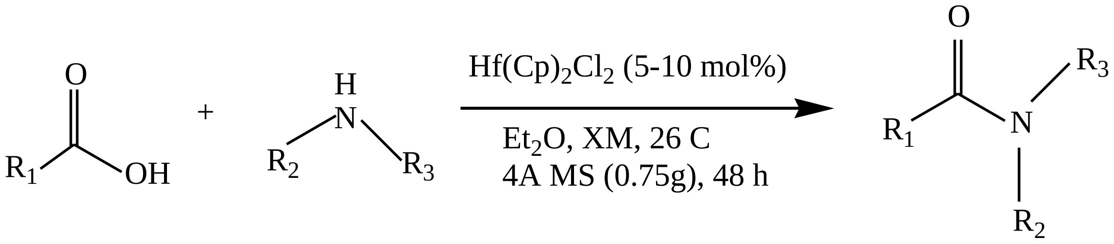
$$RNH_2 + R'COOH \xrightarrow{\text{Microwave}} R'-\overset{\overset{\Large O}{\|}}{C}-\overset{H}{N}-R$$

Helena Lundberg *et al.*,(2015) studied Hafnium-Catalyzed direct amide formation at room temperature. This study involves the metal-catalyzed protocol for the direct amidation of nonactivated carboxylic acids at ambient temperature. The mild reaction conditions, time as 90 min and employing commercial Hafnium as a catalyst gives rise to high yields of amide. When phenylacetic acid **(71)** reacts with Benzylamine **(72)** in the presence of Hafnium catalyst $[Hf(Cp)_2Cl^2$ results in amide with the yield of 71%. Different subtrates of carboxylic acid reacts with amine gives rise to corresponding amides **(73)** with good yield.



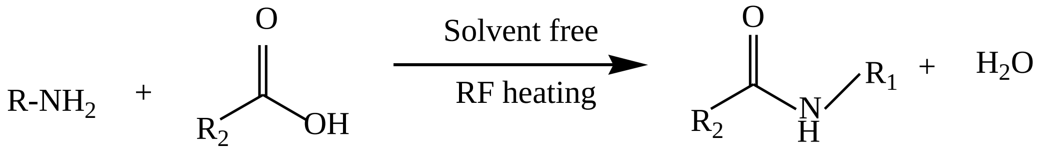
1:1 molar ratio
0.5 mmol scale

Substrate scope



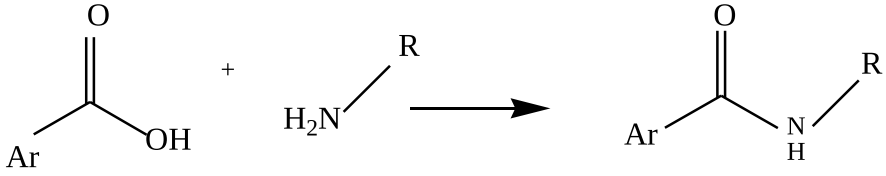
Thomas K. Houlding *et al.*,(2012) investigated direct amide formation using radiofrequency heating. This study demonstrates that the simple method for direct and solvent-free formation of amides from carboxylic acid and amides **(76)** using radiofrequency heating.

The reaction was carried out using benzylamine **(74)** and 4-phenylbutyric acid**(75)** and Nickel ferrite nano particles was used as a heat source for radiofrequency heating. Acids such as isobutyric, benzoic acid and substituted benzoic acid gives high yields than 4-phenylbutyric acid reacted with benzylamine and aniline due to low intrinsic reactivity. Different substrates of amides were obtained in appropriate yields when different carboxylic acids reacted with amines.



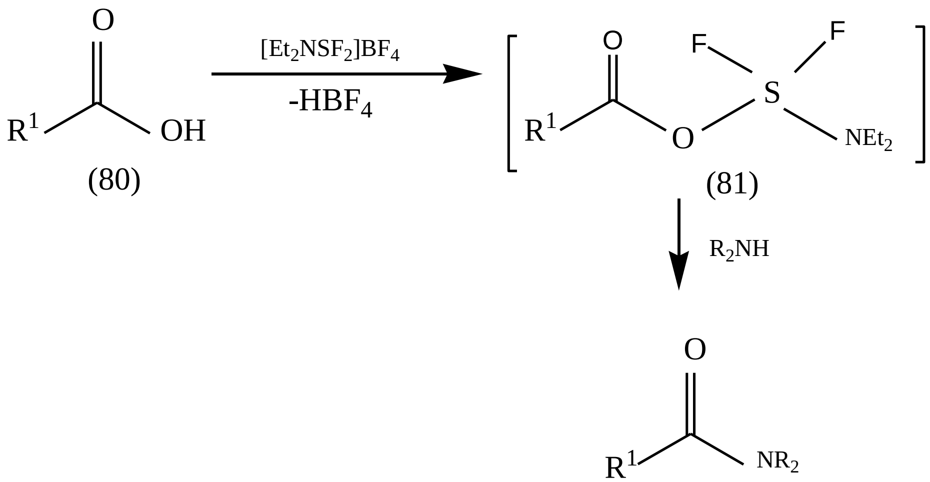
(74) (75) (76)

Danny C. Lenstra *et al.*,(2014) studied Triphenylphosphine-catalysed amide bond formation between carboxylic acids and amines. In this study the amide formation involves the reaction of unactivated carboxylic acids and amines under organocatalytic Ph_3P/CCl_4 catalyst by employing *in situ* reduction of triphenylphosphine oxide into triphenylphosphine in the presence of diethoxymethylsilane and bis(4-nitrophenyl)phosphate. When 4-nitobenzoic acid **(77)** reacts with 4-methoxybenzylamine **(78)** under catalytic conditions yields corresponding amide **(79)** of 82%. 2-(Aminomethyl)thiophene, 2-phenylethylamine and cylohexamine gave 71,96,65% conversion to corresponding amides respectively.



(77) (78) (79)

Oliver Mahe *et al.*,(2013) investigated amide formation using *in situ* activation of carboxylic acids with $[Et_2NSF_2]BF_4$. In this study, it was demonstrated that the formation of amides **(82)** through the in situ activation of carboxylic acids **(80)** with $[Et_2NSF_2]BF_4$ **(81)**. From the previous study it was demonstrated that wide range of carboxylic acid and amines gives rise to corresponding amides in up to 99% yield. The reactions were carried out under nitrogen or argon atmosphere with dry solvents under anhydrous conditions. The acid in ethyl acetate was reacted with amine under argon atmosphere. Different amides were obtained when reacting different carboxylic acid with amines.

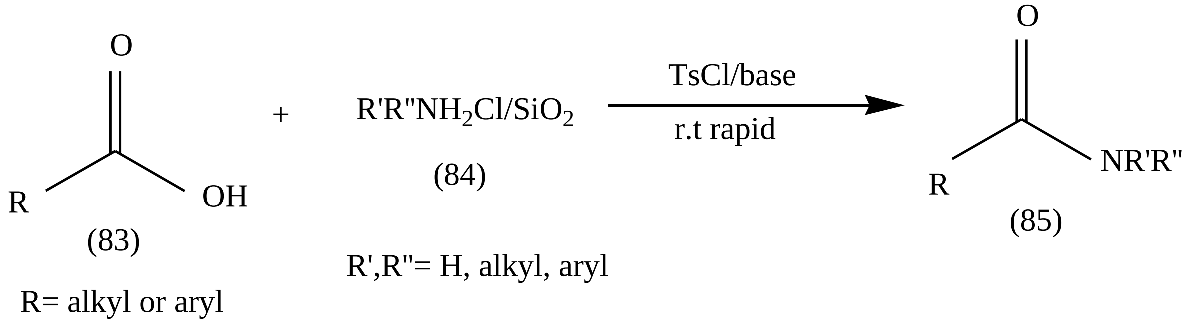


(80) (81) (82)

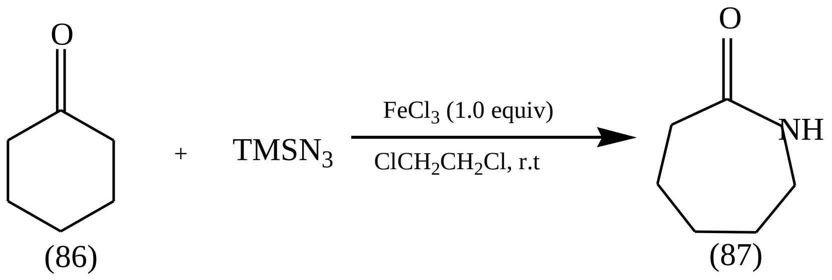
S. Funda Ekti *et al.*,(2013) studied the microwave assisted synthesis of ferrocene amides. Ferrocene carboxylic acid was derived using direct 1H-benztriazole/$SOCl_2$ methodology to prepare N-ferrocenoyl benzotriazole as a new starting material for the functionalization of ferrocene ring. N-ferrocenoyl benzotriazole reacts with mono- and di amine under microwave radiation yields mono- and di amides in high purity and good yield. Different substrates of carboxylic acid react with amine yield corresponding amides.

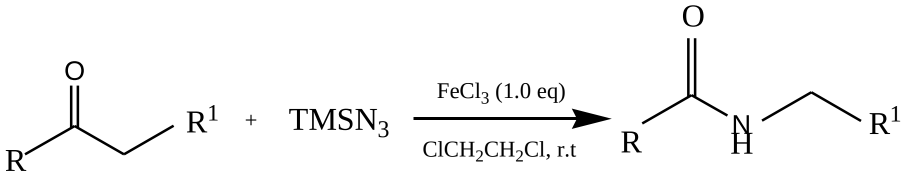
Rogerio da C. Rodrigues *et al.*,(2005) studied mild one-pot conversion of carboxylic acids to amides or esters with Ph_3P/trichloroisocyanuric acid. The reaction of trichloroisocyanuric acid and triphenylphosphine in the presence of carboxylic acid results in the formation of acid chloride. Then addition of amines or alcohols in the presence of tertiary amine yields corresponding amides or esters in excellent to good yields. In this study, it was demonstrated that carboxylic acids can be converted into acid chlorides by mixing with Ph_3P/trichloroisocyanuric acid with CH_2Cl_2 at 0℃ and on adding amines or alcohols in the presence of tertiary amine yields amide in one-pot procedure. Initially the ratio of 1.1:0.3 of RCOOH- Ph_3P-TClCA was reacted the reaction conditions of the reactions were slow and afford poor yields. The ratio of 1:1:1 showed some significant improvement in yield.

Ali Khalafi-Nezhad *et al.,*(2005) investigated efficient method for the direct preparation of amides from carboxylic acids using tosyl chloride under solvent-free conditions. This study reveals the simple, clean and efficient method for the synthesis of primary, secondary, tertiary and aromatic amides from the direct reaction of carboxylic acids and silica-supported ammonium salts, triethyl amine and tosyl chloride as condensing agent. This reaction results in high yield at room temperature. The synthesis of benzamide **(85)** involves the reaction of benzoic acid **(83)**, ammonium chloride **(84)** in the presence of tosyl chloride and triethyl amine at 100℃ had little effect. To optimize the reaction conditions several ammonium salts were used as amine source. The amidation of carboxylic acid yields corresponding amides in good yields.

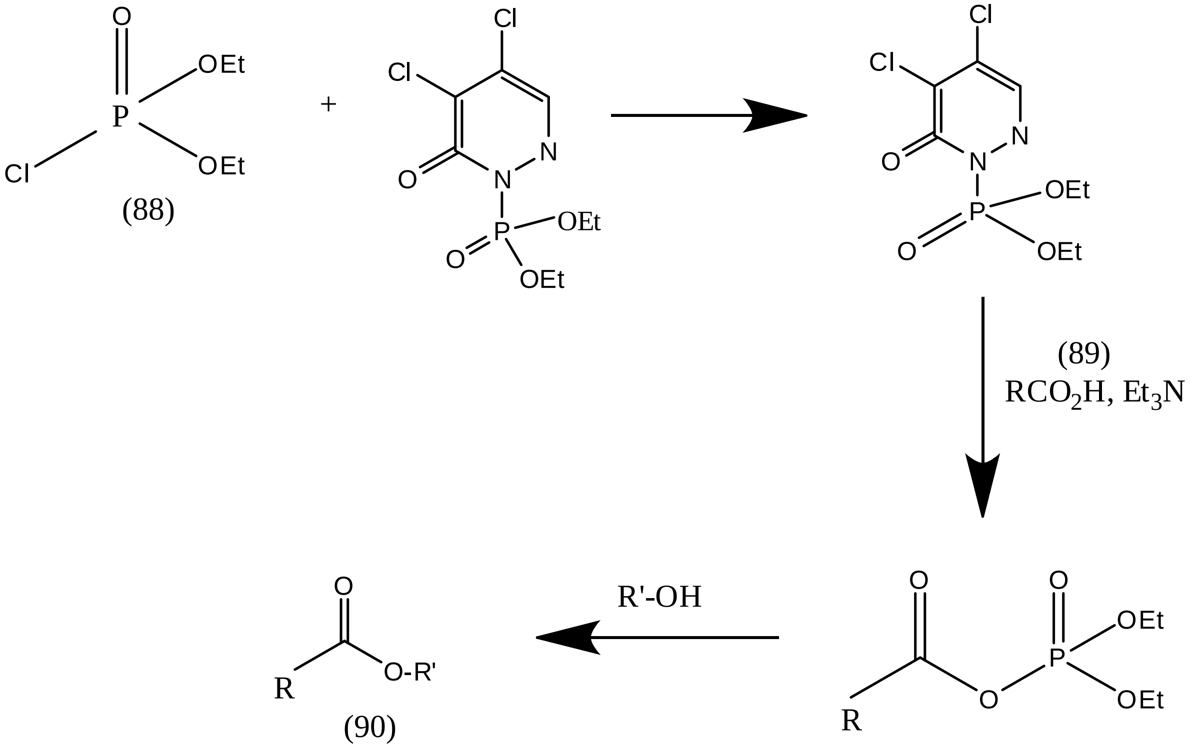


J. S. Yadav *et al.,*(2008) studied Azido-Schmidt reaction for the formation of amides, imides and lactones from ketones in the presence of $FeCl_3$. Ketones undergo smooth rearrangement with $TMSN_3$ in the presence of $Fecl_3$ under extremely mild conditions to give corresponding amides, imides and lactams in good yield with high selectivity. Acyclic ketones such as acetophenone, propiophenone,4-hydroxyacetophenone, 4-iodoacetophenone and benzophenone **(86)** undergoes a rearrangement reaction gives corresponding amides **(87)** in good yields. Among the other catalyst such as $InCl_3$, $ZrCl_4$, $YbCl_3$ and YCl_3 were studied for the amide conversion, $FeCl_3$ was found to be more effective. This reaction gives mild reaction conditions, short reaction times, easy work up and good yields.

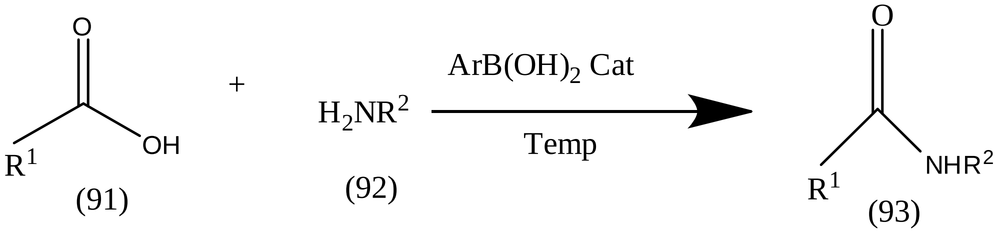




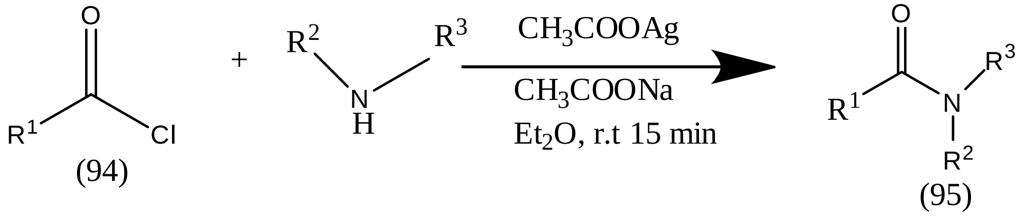
James McNulty *et al.*,(2008) studied the direct formation of esters and amides from carboxylic acids using diethyl chlorophosphate **(88)** in pyridine. An efficient method involves the activation of carboxylate-phosphate synthesis of esters from carboxylic acids **(89)** and alcohols, as well as the formation of amide and peptide derivatives. The reaction proceeds with the retention of configuration with both chiral secondary alcohols and α-amino acid derivatives. Ester **(90)** and amide products were isolated directly in high yield due to water soluble nature of the side products.



Nicolas Gernigon *et al.*,(2013) studied the solid-supported ortho-iodoarylboronic acid catalyst for direct amidation of carboxylic acids. In this study, a recyclable resin-supported derivative of 5-methoxy-2-iodophenylboronic acid was used as a heterogeneous catalyst for promoting direct amidation of aliphatic carboxylic acid **(91)** and amines **(92)**. Phenylacetic acid reacts with benzylamine gives corresponding amide **(93)** in 90% yield within 48 hr. In this reaction solid supported boronic acid catalyst was used that can be easily separated from 4A molecular sieves and recovered by double filtration strategy.

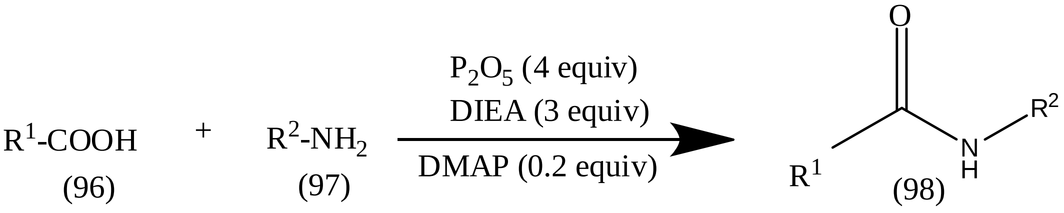


A. Leggio *et al.*,(2014) studied silver acetate assisted formation of amides **(95)** from acyl chlorides **(94)**. This study demonstrates the simple method for the aminolysis of carboxylic acid chlorides to give amides. This reaction is very useful in forming peptide bonds. N,N-diethylbenzamide was synthesized by the reaction of N-(4-nitrobenzenesulfonyl)-protected dipeptide methyl esters with N,N-Diethylamine (1 mmol), silver acetate (1 mmol) and sodium acetate (2 mmol) were added to a solution of benzoyl chloride (1 mmol) in diethyl ether (10 mL). Finally the corresponding amide **(95)**product is obtained. The silver cation assists the formation of amide, and the acetate ion and silver chloride were easily removed from the reaction.



Venkatramana Erapalapati *et al.*,(2019) studied phosphorus pentoxide for amide and peptide bond formation with minimal by-products. The formation of amide **(98)** bond from the reaction of carboxylic acids **(96)** and amines **(97)**, the reagents phosphorus pentoxide and DMAP were used. Dipeptides and amides were synthesized by using the reagent which gives 42-77% yield. In this study, the carboxylic acid reacts with amine in the presence of phosphorus pentoxide, diisopropylethylamine(DIEA) and catalytic amounts of dimethylamino pyridine

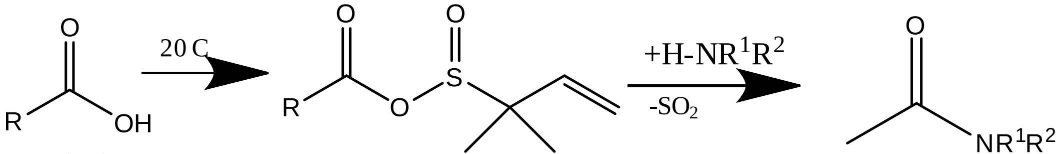
(DMAP). The coupling of aromatic or benzylic carboxylic acids with primary and secondary amines results in the corresponding amide products. Amides with electron withdrawing groups can also be obtained using P_2O_5 with relatively lower yields which is approximately 40%. This reaction protocol shows that the reagent is cheap, formation of hazardous organic by products is minimal and isolation of desired amide is quick.



(96) (97) (98)

42-77% yield

Bartosz K. Zambron *et al.*,(2013) studied the amide formation in one pot from carboxylic acids and amines via carboxyl and sulfinyl mixed anhydrides. This study shows the efficient method for the preparation of acyclic mixed anhydrides of carboxylic **(99)** and sulfinic acids. Sterically hindered 2-methylbut-3-ene-2-sulfinyl carboxylates reacts with primary and secondary amines on the carbonyl moieties results in a new method for the preparation of carboxamides **(100)**.

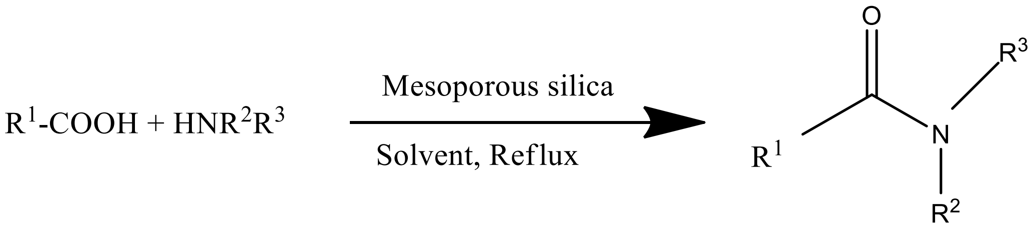


(99) (100)

Jianfei Bai *et al.*,(2013) synthesized amides in one pot from carboxylic acids and amines via Sulfinylamides. An efficient method was developed for the direct amidification of carboxylic acids via sulfinylamides performed *in situ* via the reaction of amines with propene-1-sulfinyl chloride. This protocol was applied to aliphatic acids including pivalic acid, aromatic acid and primary and secondary amines. This reaction does not induce α-epimerization.

$$R^1R^2NH \xrightarrow[\substack{R^3COOH/DMAP,\ 70\ C \\ 50\text{-}85\%}]{\substack{CH_2=CHCH_2SOCl/Et_3N \\ -60\ C\ \text{to}\ 20\ C}} R^1R^2NCOR^3 + Et_3NH^+Cl^- + CH_2=CHMe + SO_2$$

Mizuki Tamura *et al.*,(2015) studied direct amide synthesis from equimolar amounts of carboxylic acid and amine catalyzed by mesoporous silica SBA-15. This study involves the direct amidation of benzoic acid with various amines such as aniline, benzylamine, n-hexylamine and morpholine. Heterogenous catalyst mesophorus silica was used in this reaction. In the absence of catalyst SBA-15, no amide formation is obtained and however the reaction gives amide in 26% yield. The reaction proceeds in good to moderate yields except for aniline, affords amide over SBA-15 catalyst.



MATERIALS AND METHODS

3. MATERIALS AND METHODS

3.1 GENERAL

- Melting points were determined by using SAFIRE melting point apparatus.

- The Fourier transform infrared (FTIR) spectra were recorded by ART technique in a SHIMADZU spectrophotometer. Absorption frequencies were quoted in cm^{-1}.

- Nuclear Magnetic resonance (H^1 NMR and C^{13} NMR) spectra were determined by Bruker modern 400 MHz FT NMR instrument in DMSO as a solvent Tetra methyl silane as the internal reference. Chemical shifts were quoted in parts per million (ppm).

- Thin Layer Chromatography (TLC) was performed using glass plate coated with silica gel G to monitor and check the completion of each reaction.

- Ethyl alcohol; Hexane were used as the developing solvents. Spots were detected with Iodine.

- The solvents and reagents used for the synthesis were purified by standard methods.

3.2 PREPARATION OF GLUTARIC ACID 2-AMINO ACETOPHENONE SUBSTRATES

3.2.1 PREPARATION OF 3-(3-(l2-AZANEYL)-3-OXOPROPYL)-4-METHYLQUINOLIN-2(1H)-ONE-1,3-DIMETHOXY-2-METHYLBENZENE

0.1053g of Glutaric acid 2-amino acetophenone was dissolved in 1ml of Dimethyl formamide(DMF) which was taken in a round bottom flask. 0.078g of anhydrous Ferric chloride and an additional acetic acid was added to the solution contained in a round bottom flask. Then the reaction mixture was stirred continuously for 50℃ for 15 to 20 minutes. And dissolve 0.123g of 2,5-dimethoxy aniline in 1-2ml of Dimethyl formamide(DMF) which was added to the above reaction mixture. Then the reaction was refluxed at 90℃ for 6 hour 35 minutes. The reaction was monitored by thin layer chromatography (TLC). After the completion of the reaction, the mixture was kept in ice bath and ammonia solution was poured into it. The solid precipitate was obtained.

Then it was filtered, dried and recrystallized. The crude product is purified with ethyl acetate. The yield of the substance is 44.08%.

3.2.2 PREPARATION OF 3-(3-(l2-AZANEYL)-3-OXOPROPYL)-4-METHYLQUINOLIN-2(1H)-ONE-O-TOLYL-L1-SULFANE-TOLUENE

0.1053g of Glutaric acid 2-amino acetophenone was dissolved in 1ml of Dimethyl formamide(DMF) which was taken in a round bottom flask. 0.078g of anhydrous Ferric chloride and an additional acetic acid was added to the solution contained in a round bottom flask. Then the reaction mixture was stirred continuously for 50℃ for 15 to 20 minutes. And dissolve 0.201g of 2-Phenyl thio aniline in 1-2ml of Dimethyl formamide(DMF) which was added to the above reaction mixture. Then the reaction was refluxed at 90℃ for 9 hour 40 minutes. The progress of the reaction was monitored by thin layer chromatography (TLC). After the completion of the reaction, the mixture was kept in ice bath and ammonia solution was poured into it. The solid precipitate was obtained. Then it was filtered, dried and recrystallized. The crude product was purified with ethyl acetate. The yield of the substance is 28.3%.

3.2.3 PREPARATION OF 3-(2-(l2-AZANEYL)-2-OXOETHYL)-4-PHENYLQUINOLIN-2(1H)-ONE-TOLUENE

0.1053g of Succinic acid 2-amino benzophenone was dissolved in 1ml of Dimethyl formamide(DMF) which was taken in a round bottom flask. 0.078g of anhydrous Ferric chloride and an additional acetic acid was added to the solution contained in a round bottom flask. Then the reaction mixture was stirred continuously for 50℃ for 15 to 20 minutes. And dissolve 0.090 ml of aniline in 1-2ml of Dimethyl formamide(DMF) which was added to the above reaction mixture. Then the reaction was refluxed at 90℃ for 16 hour. The progress of the reaction was monitored by thin layer chromatography (TLC). After the completion of the reaction, the mixture was kept in ice bath and ammonia solution was poured into it. The solid precipitate was obtained. Then it was filtered, dried and weighed. The yield of the substance is 67%.

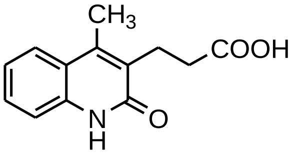
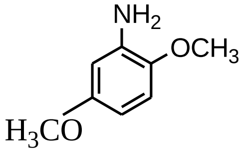
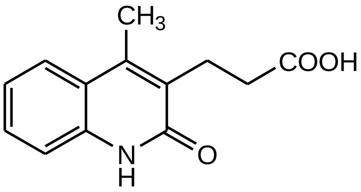
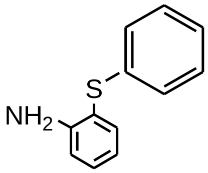
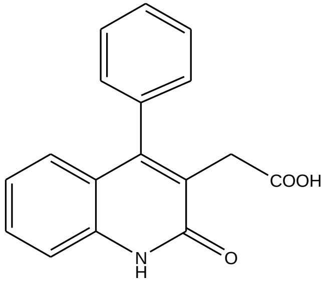
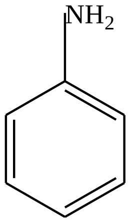
RESULTS AND DISCUSSION

4. RESULTS AND DISCUSSION

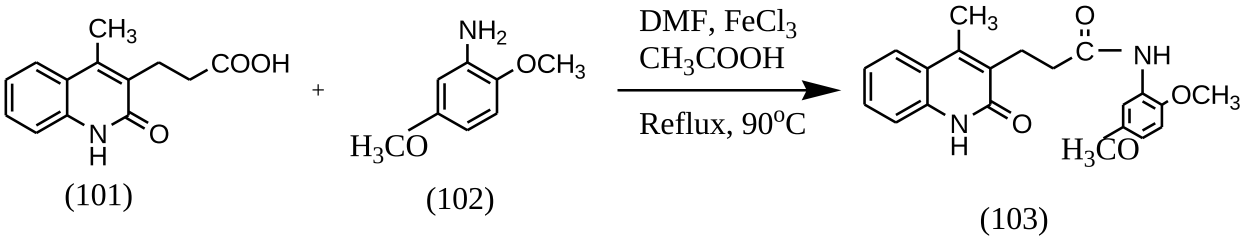
In the present work, the reaction of Glutaric acid 2-amino acetophenone and Succinic acid 2- amino benzophenone with different amines such as 2,5-dimethoxy aniline, 2-phenyl thio aniline and aniline in the presence of $FeCl_3$ catalyst at 90^{o}C to yield corresponding amides.

The yield and melting points of the synthesized compounds were listed in the **Table-I.**

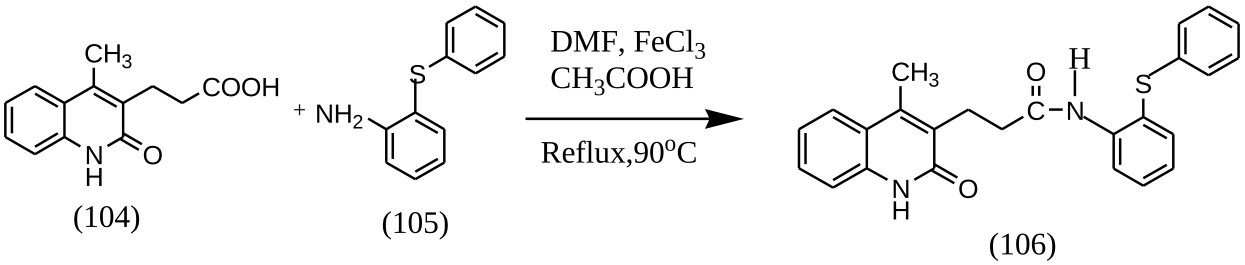
Table I: The yield and melting point of synthesized compounds.

S. NO	REACTANT (A)	REACTANT (B)	COLOUR	MELTING POINT (° C)	YIELD (%)
1.			Bluish black	156°C	44.08%
2.			Brown	98°C	28.3%
3.			Brown	192^{o}C	67%

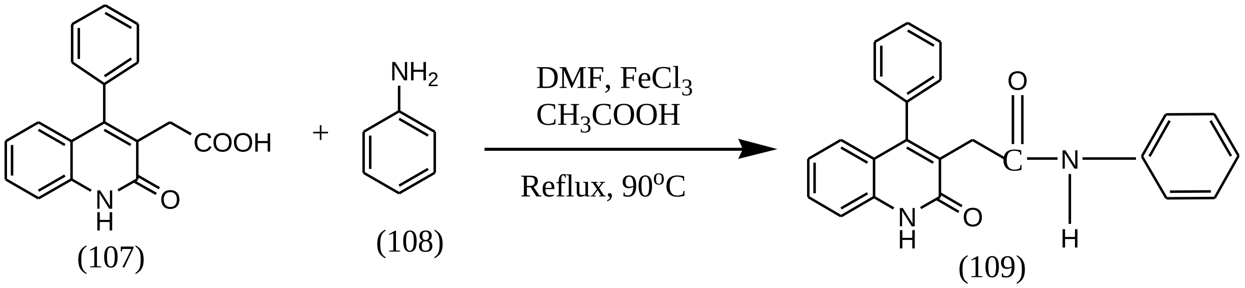
Scheme I



Scheme II



Scheme III



The above reactions were carried out by stirring the mixture of Glutaric acid 2-amino acetophenone and Succinic acid 2-amino benzophenone in DMF with $FeCl_3$ and acetic acid separately at 50°C for 10-15 minutes. Then an amine 2,5-dimethoxy aniline, 2-phenyl thio aniline and aniline were added separately to the each reaction mixture and refluxed at 90°C for 6 hour 35 minutes, 9 hour 40 minutes and 16 hour respectively. The completion of reaction was monitored by Thin layer chromatography (TLC). After the completion of the reaction, the reaction mixture was kept in ice bath and ammonia solution was poured into it. The solid precipitate was obtained. Then it was filtered, dried and recrystallized. The crude product was purified with ethyl acetate. The yield and melting points of the product are given in the **table I.**

4.2 CHARACTERZATION OF SYNTHESIZED COMPOUND

The synthesized compounds were characterized by **FT-IR** and **H^1 NMR** spectrum.

4.2.1 FT-IR ANALYSIS

The FT-IR spectrums of the synthesized compound were given in the **Figures 1, 2 & 3.**

4.2.1.a 3-(3-(l2-AZANEYL)-3-OXOPROPYL)-4-METHYLQUINOLIN-2(1H)-ONE-1,3-DIMETHOXY-2-METHYLBENZENE

The FT-IR spectrum of 3-(3-(l2-azaneyl)-3-oxopropyl)-4-methylquinolin-2(1H)-one-1,3-dimethoxy-2-methylbenzene is shown in the **Figure 1** indicated a band at 3313.71 cm^{-1} that is attributed to amide –NH stretching. A sharp peak at 1508.33 cm^{-1} shows C=C stretching in aromatic rings. A peak at 1222.87 cm^{-1} indicates C-N stretching. The band at 1031.92 cm^{-1} is attributed to C-O stretching at the methoxy oxygen. The N-H out of plane bending is observed at 842.89 $cm^{-1.}$

4.2.1.b 3-(3-(l2-AZANEYL)-3-OXOPROPYL)-4-METHYLQUINOLIN-2(1H)-ONE-O-TOLYL-l1-SULFANE-TOLUENE

The FT-IR spectrum of 3-(3-(l2-azaneyl)-3-oxopropyl)-4-methylquinolin-2(1H)-one-o-tolyl-l1-sulfane-toluene is shown in the **Figure 2.** A peak at 3469.94 cm^{-1} indicates –NH stretching. The sharp band at 1608.63 cm^{-1} is attributed to aromatic C=C stretching. A peak at 1479.40 cm^{-1} showed $–CH_3$ bending vibration. The band appears at 1309.67 cm^{-1} is attributed to –CH bending. The peak at 744.52 cm^{-1} indicates C-N ring stretching. The C-C stretching is observed at 578.64 cm^{-1}.

4.2.1.c 3-(2-(l2-AZANEYL)-2-OXOETHYL)-4-PHENYLQUINOLIN-2(1H)-ONE-TOLUENE

The FT-IR spectrum of 3-(2-(l2-azaneyl)-2-oxoethyl)-4-phenylquinolin-2(1H)-one-toluene is shown in the **Figure 3.** The peak at 3402.78 cm^{-1} is attributed to –NH stretching vibrations. A sharp peak at 3057.58 cm^{-1} indicates the C-H stretching. A peak at 1644.02 cm^{-1} showed C=O stretching vibrations. N-H bending vibration is observed at 1556.27 cm^{-1}. A band at 1497.45 is attributed to C=C stretching. A peak at 1386.57 cm^{-1} indicates the presence of C-N stretching. A band at 672.071 is attributed to out of plane C-H bending.

FIGURE 1: FT-IR spectrum of 3-(3-(l2-azaneyl)-3-oxopropyl)-4-methylquinolin-2(1H)-one-1,3-dimethoxy-2-methylbenzene

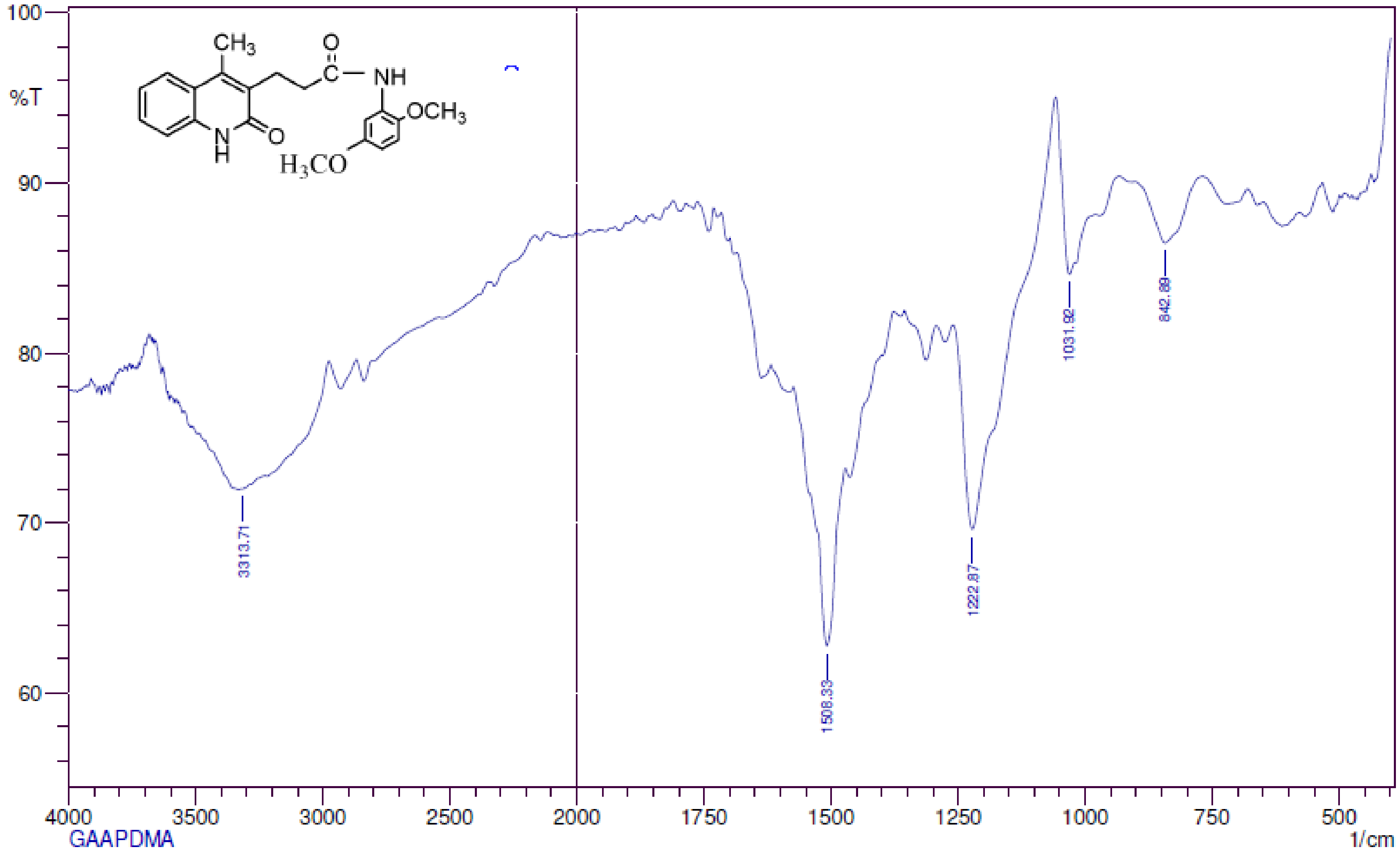


FIGURE 2: FT-IR spectrum of 3-(3-(l2-azaneyl)-3-oxopropyl)-4-methylquinolin-2(1H)-one-o-tolyl-l1-sulfane-toluene

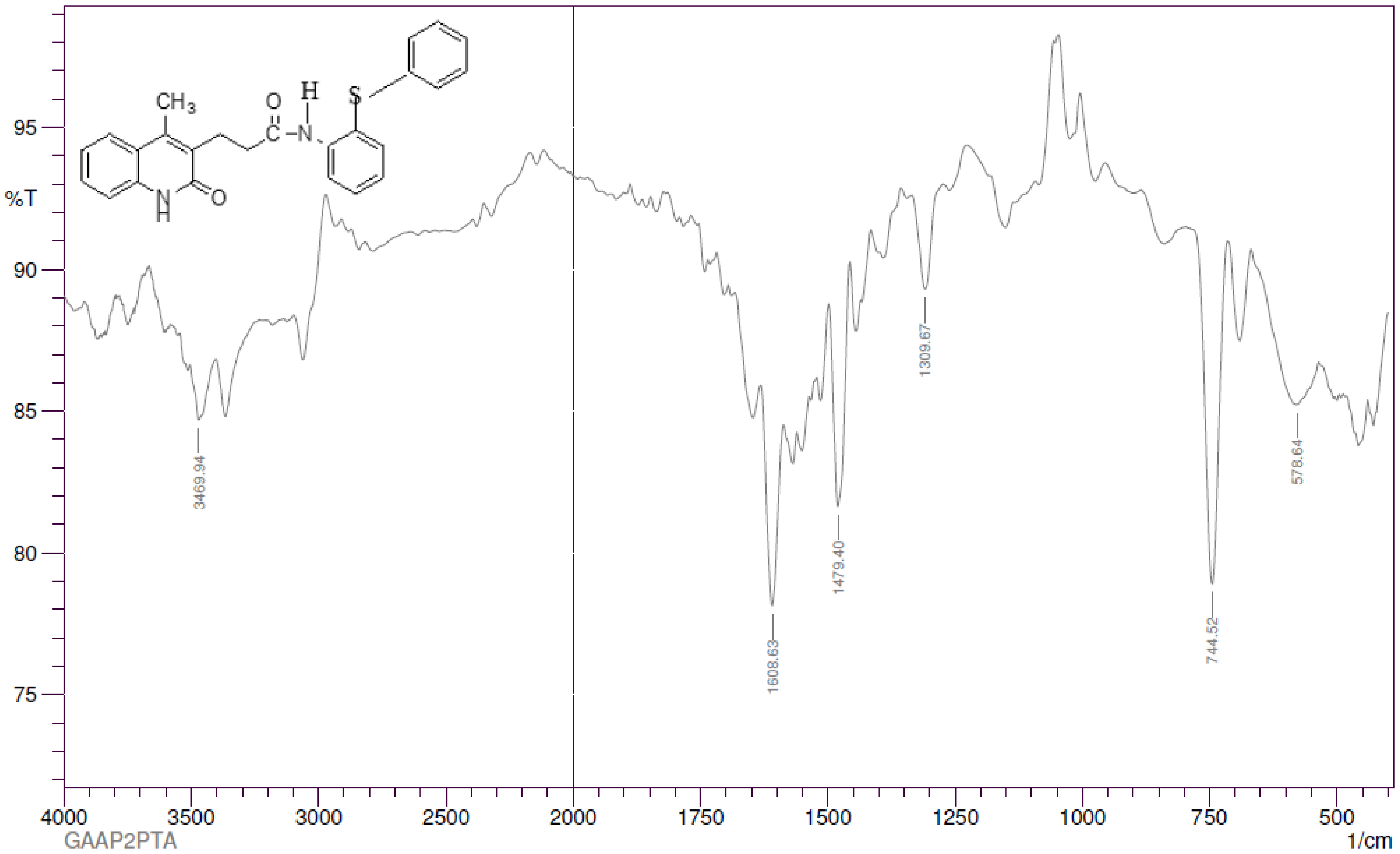
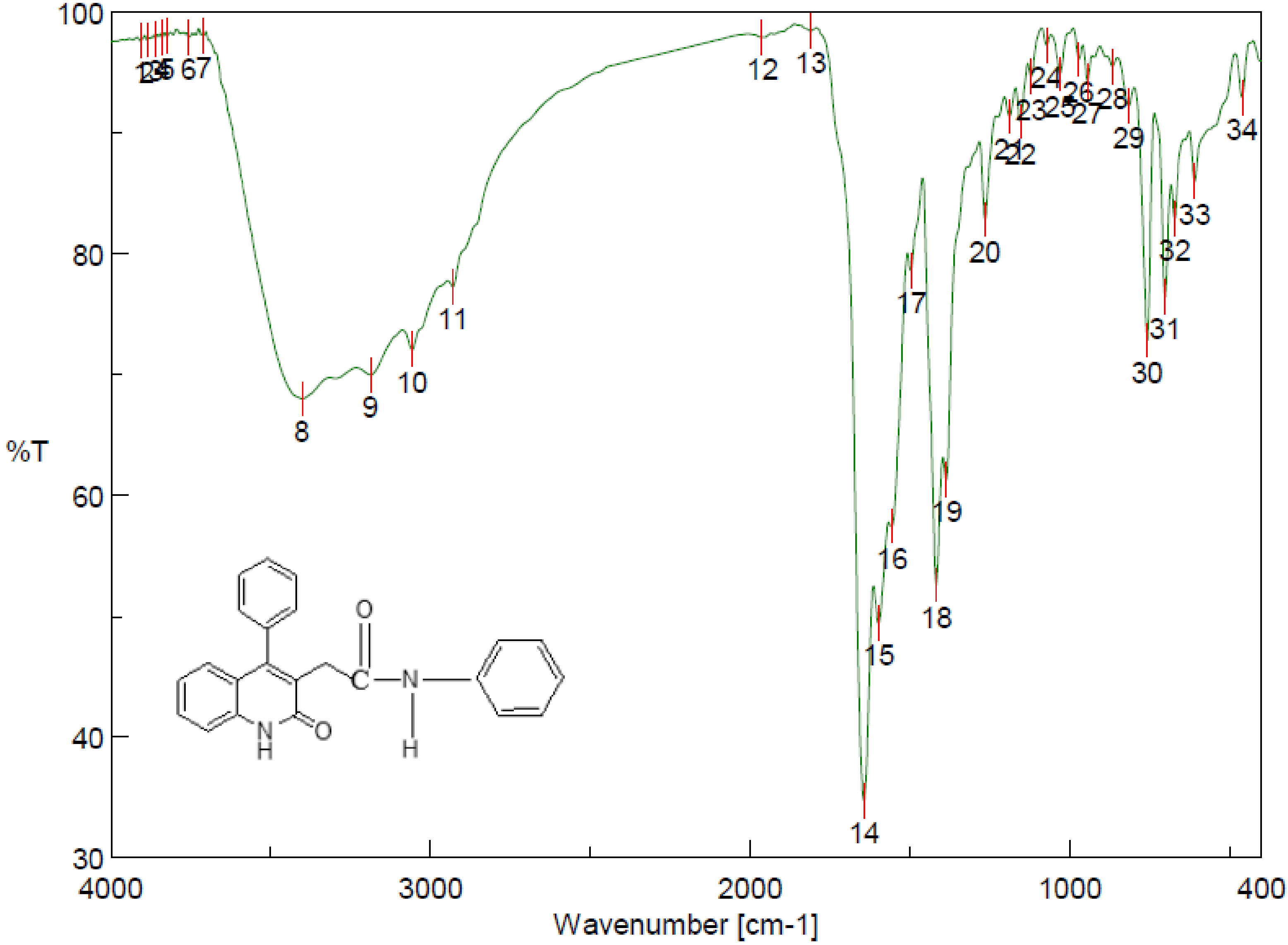


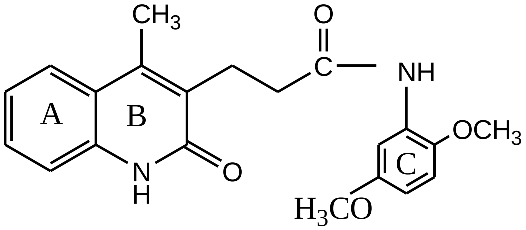
FIGURE 3: FT-IR spectrum of 3-(2-(l2-azaneyl)-2-oxoethyl)-4-phenylquinolin-2(1H)-one-toluene



4.2.2 NMR analysis

The structures of all the synthesized compounds are confirmed by NMR spectroscopy. The NMR spectrum is recorded using DMSO-d_6 solvent.

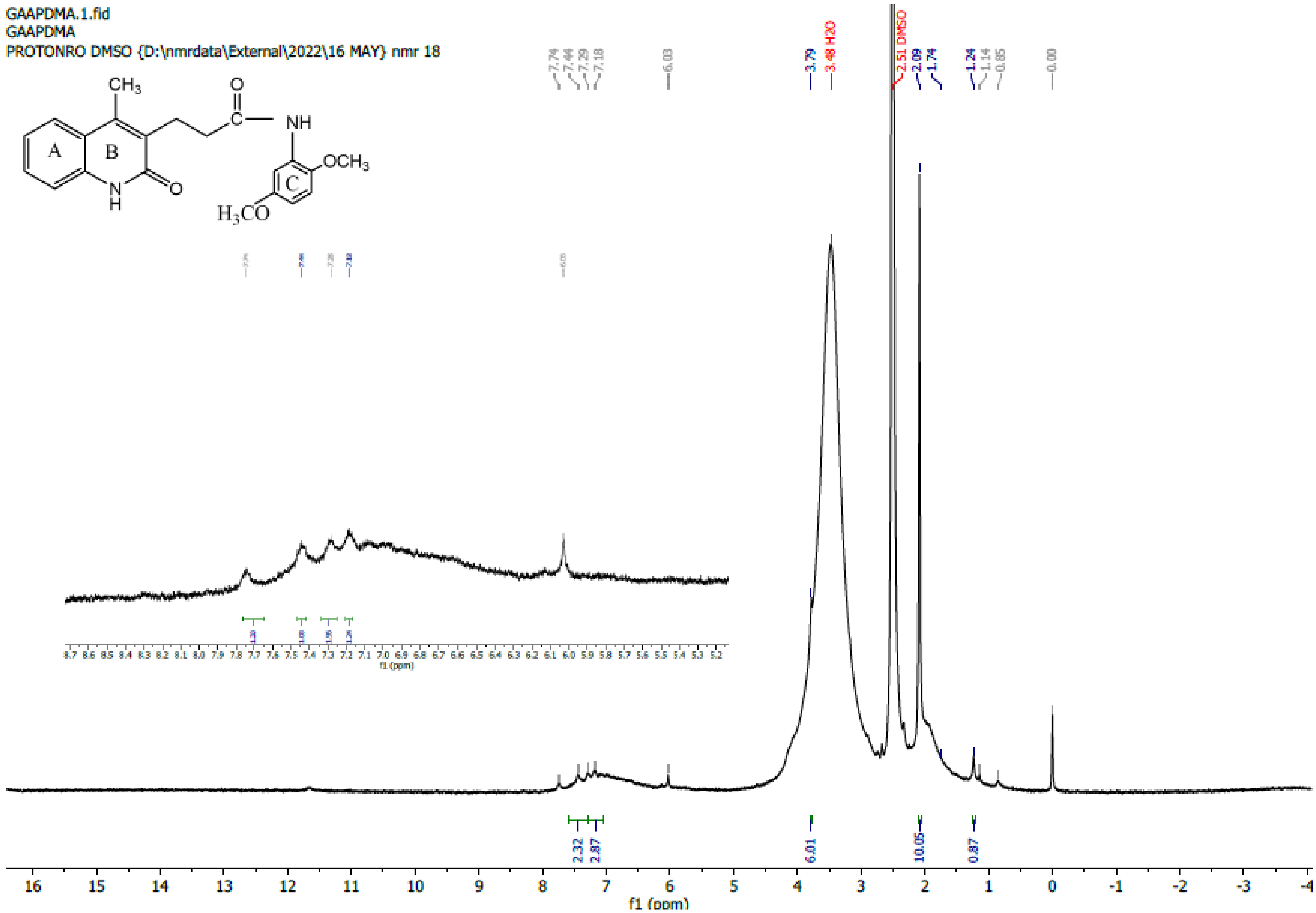
4.2.2.a H^1 NMR analysis of 3-(3-(l2-azaneyl)-3-oxopropyl)-4-methylquinolin-2(1H)-one-1,3-dimethoxy-2-methylbenzene



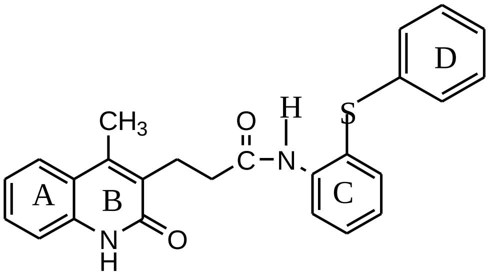
The H^1 NMR spectrum of the synthesized compound 3-(3-(l2-azaneyl)-3-oxopropyl)-4-methylquinolin-2(1H)-one-1,3-dimethoxy-2-methylbenzene is shown in the **Figure 4.** It showed various signals in the presence of DMSO-d_6 solvent.

- The peak at δ 7.18-7.44 shows the presence of four protons of the aromatic ring A. **(Pavia *et al.,*)**
- The peak at δ 7.44 indicated the presence of –NH proton of the aromatic ring B.
- In aromatic ring C, electron-donating group –OCH_3 is attached, which increases the shielding of hydrogen atoms in the ring causing them to move towards upfield. So the peak is shifted to the region of δ 2.09. The peak at δ 2.09 is attributed to six protons present in methoxy group and four protons present in methylene. **(Pavia *et al.,*)**
- The peak at δ 1.24 shows the presence of methyl protons. **(Pavia *et al.,*)**
- Due to shielding effect, the three aromatic protons in the ring C shift the peak to δ 3.79. **(Pavia *et al.,*)**
- The –NH proton attached to C=O shows the peak at δ 3.79. **(Pavia *et al.***

FIGURE 4: H^1 NMR spectrum of 3-(3-(l2-azaneyl)-3-oxopropyl)-4-methylquinolin-2(1H)-one-1,3-dimethoxy-2-methylbenzene



4.2.2.b H^1 NMR analysis of 3-(3-(l2-azaneyl)-3-oxopropyl)-4-methylquinolin-2(1H)-one-o-tolyl-l1-sulfane-toluene



The H^1 NMR spectrum of the synthesized compound 3-(3-(l2-azaneyl)-3-oxopropyl)-4-methylquinolin-2(1H)-one-o-tolyl-l1-sulfane-toluene is shown in the **Figure 5 & 6.** It showed various signals in the presence of DMSO-d_6 solvent.

- The peak at δ 4.41 is attributed to –NH proton of the aromatic ring B. **(Pavia *et al.,*)**
- The singlet peak at δ 8.28 is assigned to –NH proton of the amide substrate. **(Pavia *et al.,*)**
- The peak at δ 7.26 is attributed to five aromatic protons of the ring D. **(Pavia *et al.,*)**
- The peak at δ 5.37, 6.59, 6.61 indicates the presence of four protons of the aromatic ring C **(Pavia *et al.,*)**
- The peak at δ 6.81, 7.29 is attributed to four protons in the aromatic ring A. **(Pavia *et al.,*)**
- The peak at δ 0.85, 1.15, 1.23 shows the presence of methyl protons attached to the aromatic ring B. **(Pavia *et al.,*)**
- The singlet peak at δ 2.09 is attributed to two methylene protons attached to the aromatic ring B. **(Pavia *et al.,*)**

FIGURE 5: H^1 NMR spectrum of 3-(3-(l2-azaneyl)-3-oxopropyl)-4-methylquinolin-2(1H)-one-o-tolyl-l1-sulfane-toluene

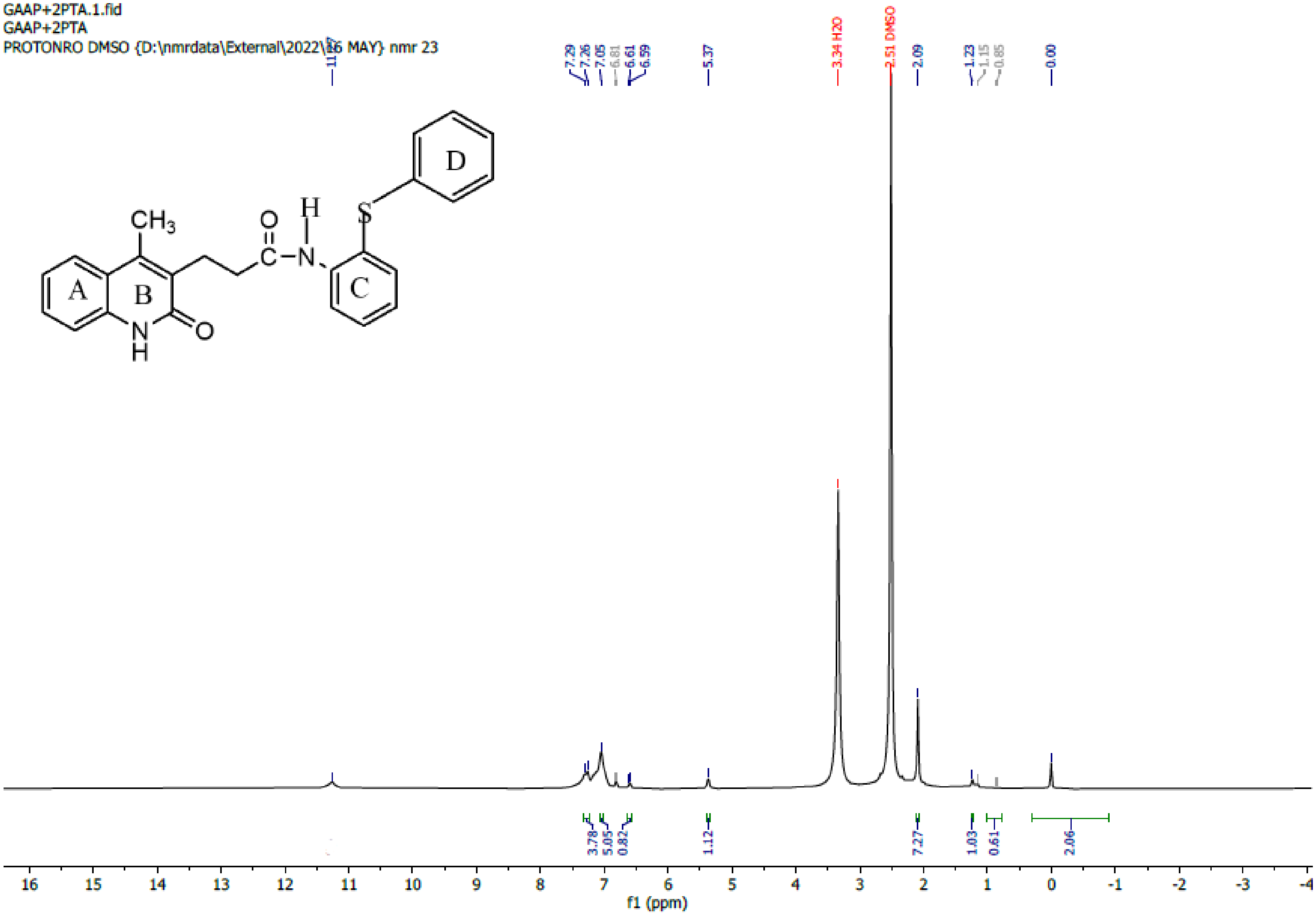
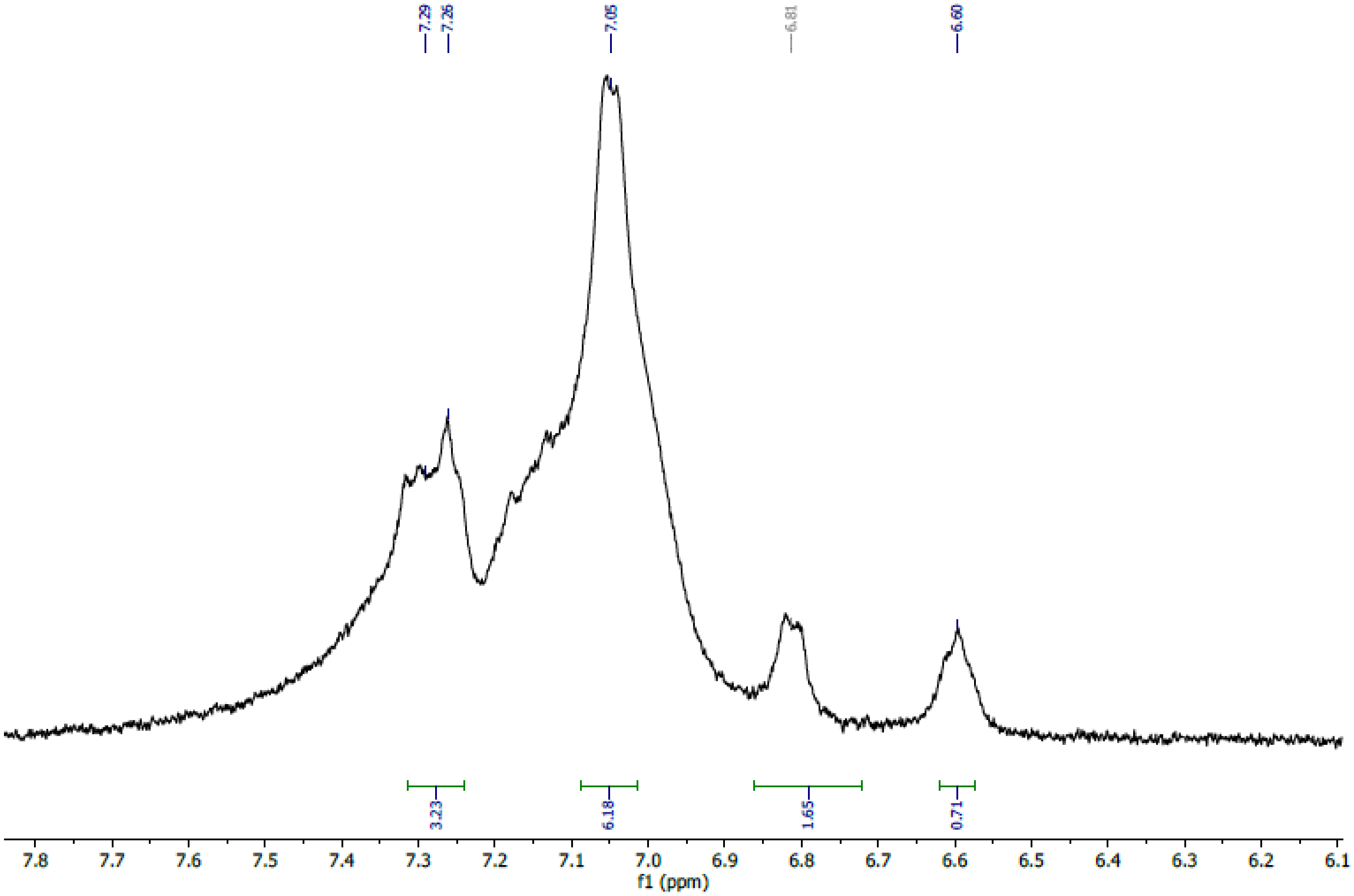
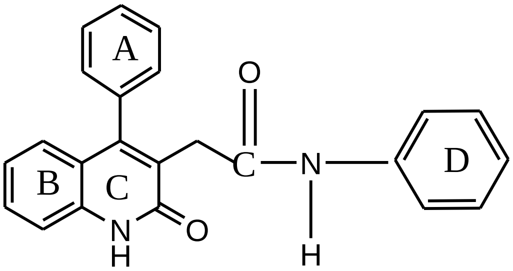


FIGURE 6: Expanded H^1 NMR spectrum of 3-(3-(l2-azaneyl)-3-oxopropyl)-4-methylquinolin-2(1H)-one-o-tolyl-l1-sulfane-toluene



4.2.2.c H^1 NMR analysis of 3-(2-(l2-azaneyl)-2-oxoethyl)-4-phenylquinolin-2(1H)-one-toluene



The H^1 NMR spectrum of the synthesized compound 3-(2-(l2-azaneyl)-2-oxoethyl)-4-phenylquinolin-2(1H)-one-toluene is shown in the **Figure.7, 8 & 9.** It showed various signals in the presence of DMSO-d_6 solvent.

- The quartet peak at δ 4.0-4.01 is assigned to the –NH proton of the aromatic ring C. **(pavia *et al.,*)**
- The singlet peak at δ 8.26 is attributed to the –NH proton of the amide substrate**.(pavia *et al.,*)**
- The multiplet between δ 7.07-7.39 indicates the presence of fifteen protons in the aromatic ring A, B and D. **(Pavia *et al.,*)**
- The singlet peaks at δ 2.88 and is attributed to methylene (-CH_2) proton near to C=O and proton.

FIGURE 7: H^1 NMR spectrum of 3-(2-(l2-azaneyl)-2-oxoethyl)-4-phenylquinolin-2(1H)-one-toluene

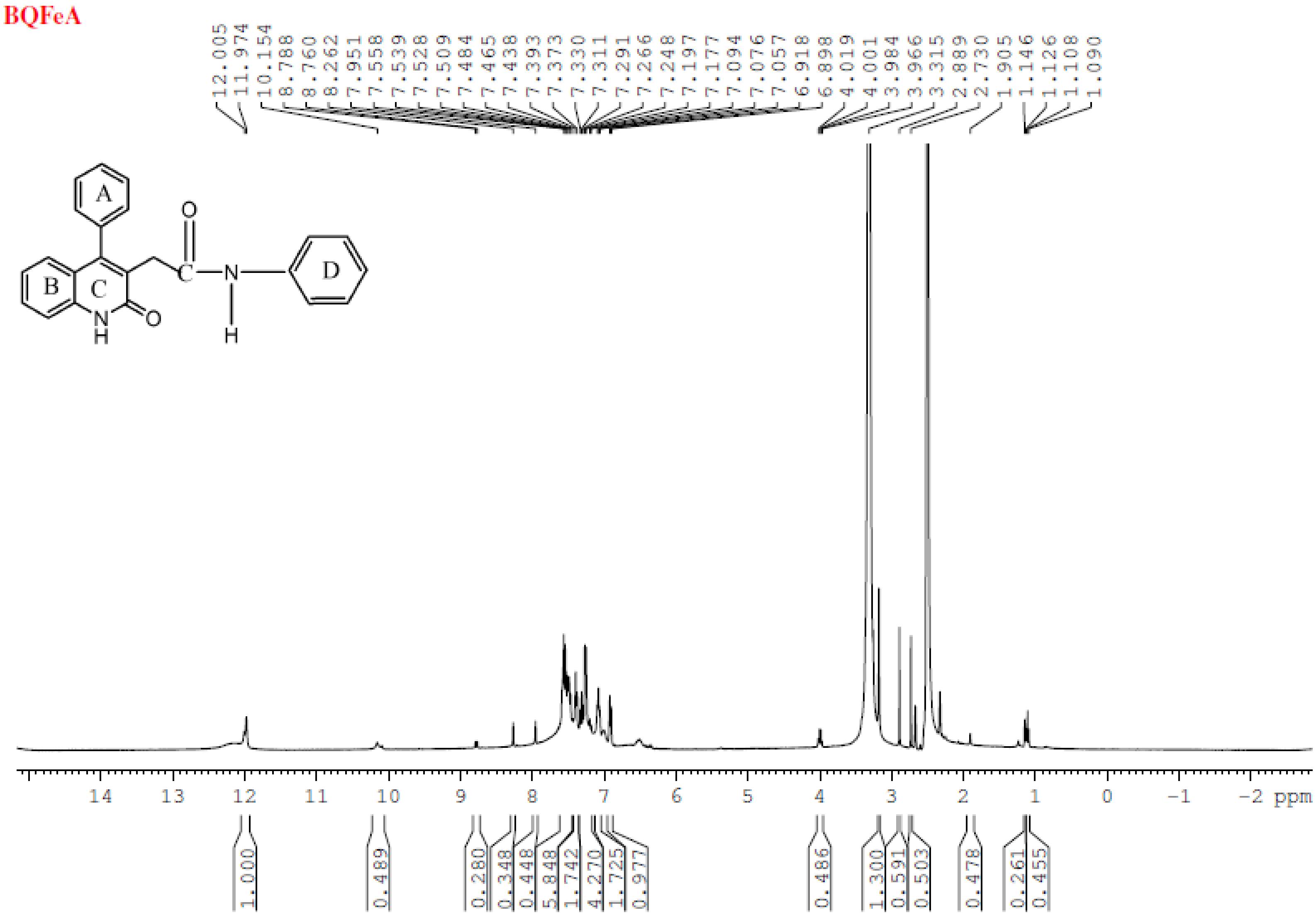


FIGURE 8: Expanded H^1 NMR spectrum of 3-(2-(l2-azaneyl)-2-oxoethyl)-4-phenylquinolin-2(1H)-one-toluene

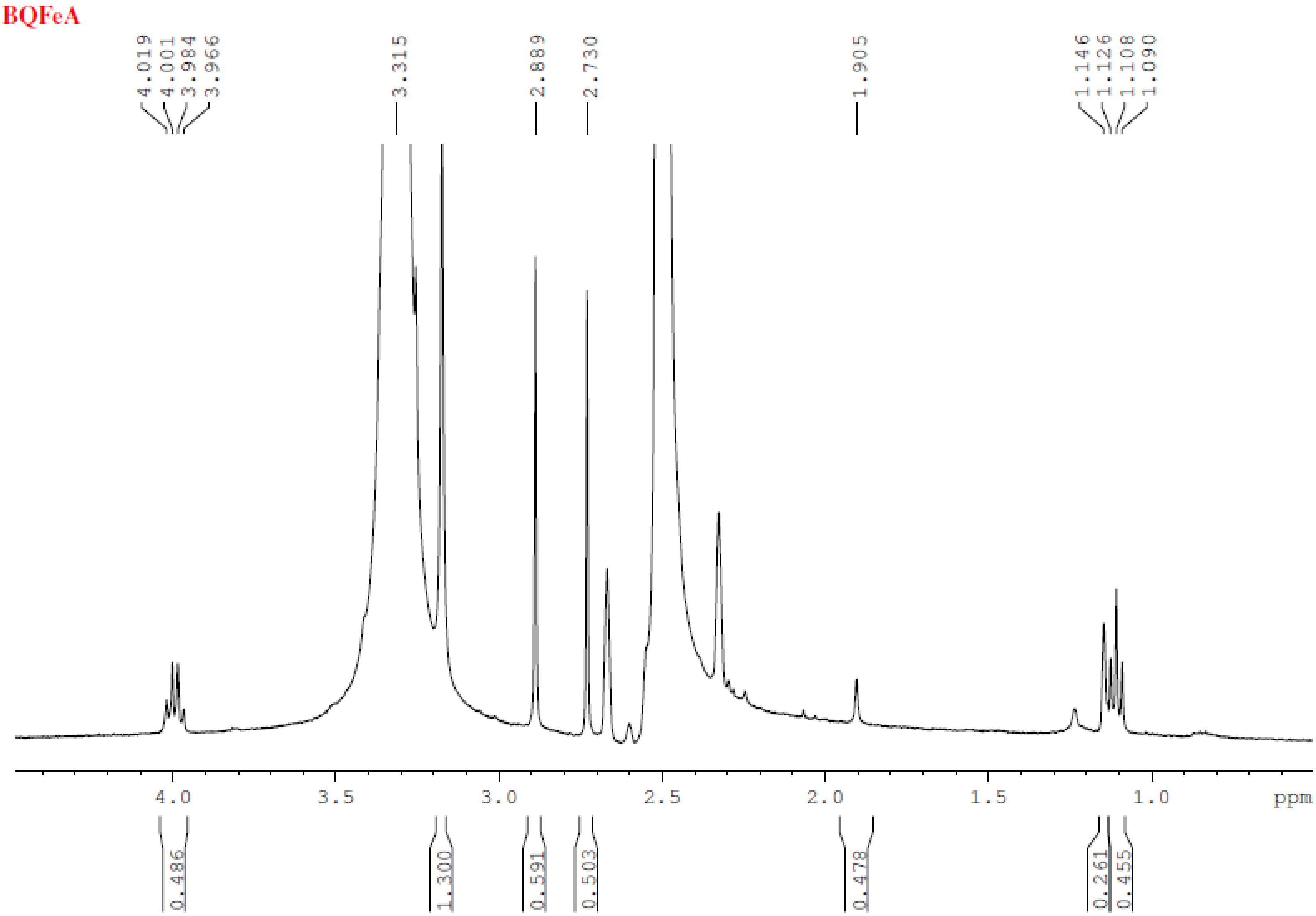
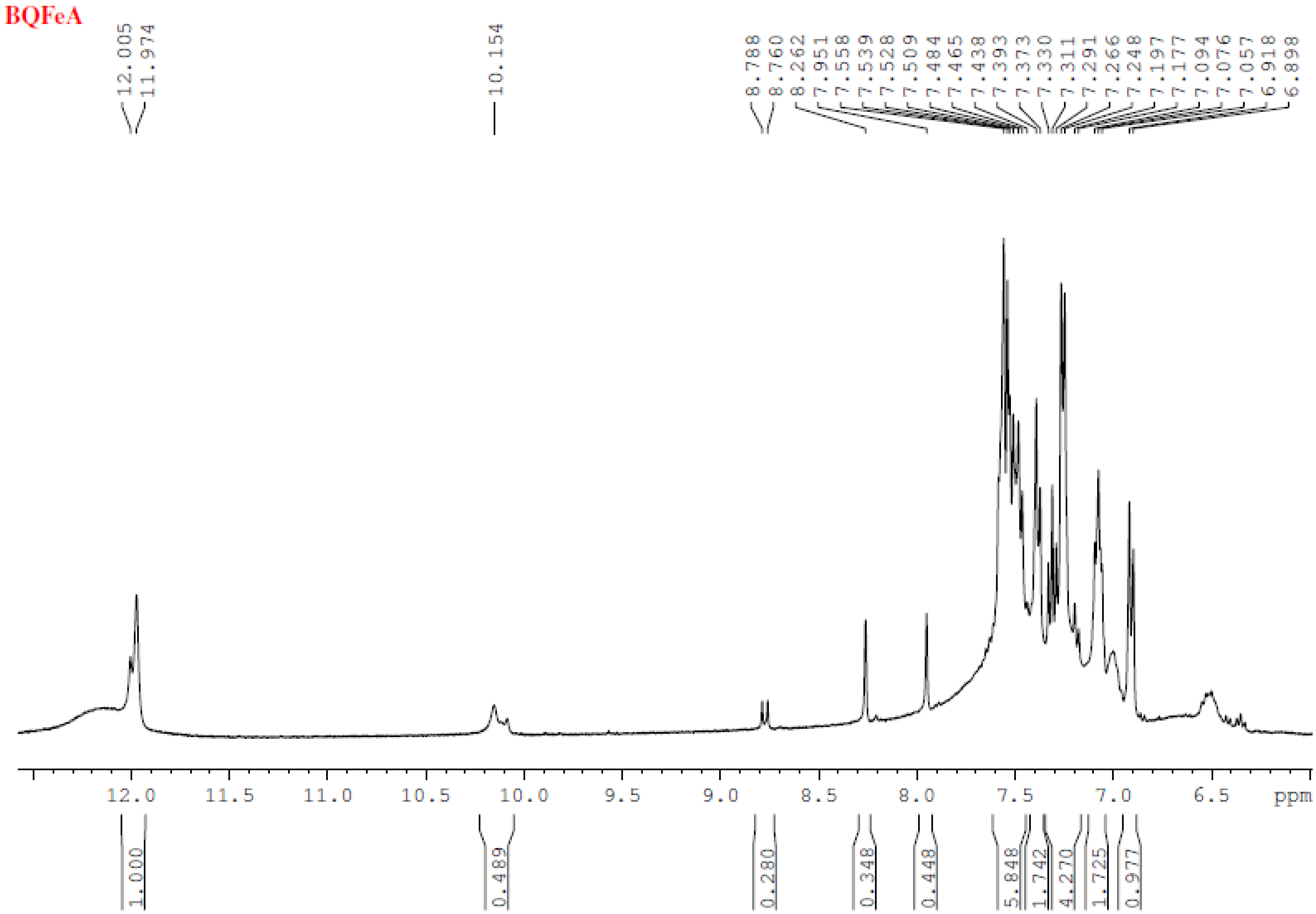


FIGURE 9: Expanded H^1 NMR spectrum of 3-(2-(l2-azaneyl)-2-oxoethyl)-4-phenylquinolin-2(1H)-one-toluene



SUMMARY AND CONCLUSION

5. SUMMARY AND CONCLUSION

The results of synthesis of Glutaric acid 2-amino acetophenone and Succinic acid 2-amino acetophenone based amides are summarized below.

- The amidation of Glutaric acid 2-amino acetophenone and Succinic acid 2-amino acetophenone in DMF and $FeCl_3$ catalyst with 2,5-dimethoxy aniline, 2-phenyl thio aniline and aniline at 90°C resulted in corresponding amides.
- The presence of the functional group in a synthesized compound is identified by FT-IR spectroscopy.
- The structure of the synthesized compound is confirmed by H^1 NMR spectrum.
- This study involves non-toxic, cheaper, greener and environmentally friendly catalyst $FeCl_3$.
- The importance of amide bond should find extensive use in organic and medicinal chemistry.

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