EXPLORATIVE STUDIES ON CARBON-NITROGEN (C-N) BOND FORMATION AND SYNTHESIS OF NITROGEN CONTAINING HETEROCYCLIC COMPOUNDS

A Thesis Submitted to the University of North Bengal

For the award of

Doctor of Philosophy (Ph.D)

In

Chemistry

By

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Research Guide

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August, 2018

Dedicated to my Parents

And my family members

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DECLARATION

I declare that the research work embodied in this thesis entitled " EXPLORATIVE STUDIES ON CARBON-NITROGEN (C-N) BOND FORMATION AND SYNTHESIS OF NITROGEN CONTAINING HETEROCYCLIC COMPOUNDS" has been accomplished in the Department of Chemistry, University of North Bengal, India- 734013, under the guidance of Dr. Pranab Ghosh, Professor, Department of Chemistry, University of North Bengal. To the best of my belief this thesis or any part of it has not been formed the basis for the award of any degree previously.

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CERTIFICATE

This is to certify that the thesis entitled "Explorative studies on carbon-nitrogen (C-N) bond formation and Synthesis of nitrogen containing heterocyclic compounds" submitted by Sri. Rakesh Ranjan Chakraborty for the award of Ph.D degree of the University of North Bengal, has carried out the entire research work under my supervision at the Department of Chemistry, University of North Bengal, Darjeeling, West Bengal, India -734013.

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Acknowledgement

This is the opportunity to express my sincerest gratitude to my supervisor, Prof. Pranab Ghosh, Department of Chemistry, University of North Bengal, Darjeeling, whose continuous support throughout my research work with his knowledge and patience made this research work successful. It is a huge honour for me to work with Prof.Pranab Ghosh

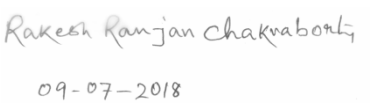
This thesis is a compilation of research work so far I have pursued during the period from 2014 to 2018 at the Department of Chemistry, University of North Bengal. Therefore, I would like to thank all the faculty members of the department of chemistry, University of North Bengal for their co operation during my research tenure. I would like to thank all the non-teaching staff of the department of chemistry, University of North Bengal, for their cooperation in all ways.

I would like to express my sincere gratitude to UGC, New Delhi, for financial assistance.

I am indebted to all of my lab-mates and fellow researchers for their cooperation, guidance and inspiration, which made me a better and enriched person and now I have the opportunity to offer gratitude to all of them.

I am indebted to my parents for their continuous inspiration and trust on me for the work I have undertaken. I offer my deep gratitude to all of my family members for their perpetual support which has made it possible for me to pursue my research work.

In addition, I wish to thank all brothers, sisters and friends of University of North Bengal.



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Abstract

General introduction of C-N bond formation and synthesis of N-containing heterocyclic compounds, their activity and scope.

The construction of the C-N bonds of aromatic compounds is particularly important in the field of medicinal chemistry. C-N bond formation reaction is thermodynamically more favourable than C-C bond formation. The construction of C-N bond has significant importance because it introduces nitrogen atom in organic molecules. Nitrogen containing compounds are extremely important because of their abundance in various natural products and in the synthetic organic compounds that show interesting biological activities. Nitrogen containing organic compounds has gained a considerable amount of attention in synthetic organic chemistry because of its several application in pharmaceutical and agrochemical industries. Beside this, it also plays a role in constructing of naturally occurring biological active compounds like amino acids, naturally occurring heterocyclic compounds, drugs etc. Extensive work has been done on the formation of C-N bond and exploring the importance of nitrogen containing compounds. The importance of C-N bond and broad spectrum application of nitrogen containing compounds compels author to carry out the methodological work on carbon-nitrogen bond formation and thereby synthesizing some nitrogen containing compounds.

Chapter- Ⅰ: One-pot synthesis of pyrazines from ethylenediamine and 1, 2-diketone or its analogues.

Section- A: Chapter I (section-A) deals with methodological literature review on pyrazine and its synthetic development in recent years. The detail literature survey in this field reveals that there is still a requirement for the easy, green and new methodology for the synthesis of pyrazine derivatives.

Section-B: Chapter Ⅰ(section-B) described the present work, which is the Clean and Green approach for one-pot synthesis of pyrazine from ethylenediamine and 1, 2-diketone or Its analogues under neat reaction condition. The mixture of ethylenediamine and 1, 2-diketones or with α-hydroxy ketone or with α-bromo ketone was kept on magnetic stirrer at room temperature that produced pyrazine derivatives. The reaction was extended to different substituted 1, 2-diketone and found satisfactory result.

Section-C: Chapter Ⅰ(section-C) has also described the present work, which is the **One-pot synthesis of pyrazines from ethylenediamine and 1, 2-diketone or its analogues by efficient silica-gel catalyst.** The synthesis of pyrazines was carried out by mixing ethylenediamine and 1, 2-diketone or its analogues on silica-gel and keeping the mixture on magnetic stirrer at room temperature.

Chapter-Ⅱ: Synthesis of Nitriles from Aldehydes and Hydroxylamine hydrochloride on silica-gel

Section-A: Section A deals with methodological literature review on nitriles, synthetic protocol and its applications. Nitriles are important intermediates for the functional group transformation and synthesis of heterocyclic compounds. During last decades, several catalytic system has been explored for the oxidative transformation of nitrile from different functional groups. Due to the draw-backs of the existing methodologies, some new protocols were required.

Section-B: Chapter Ⅲ (section-B) deals with one-pot transformation of aldehydes into nitriles on silica-gel. The reactions were carried out by mixing aldehyde (1 mmol) and hydroxylamine hydrochloride (1.2 mmol) to 1gm silica-gel and grind it for a few minutes. The resulting mixture was kept on hot magnetic stirrer for four hours at 83°C and got 87% nitrile. We applied this

methodology to different aldehydes (aliphatic, aromatic, substituted aldehyde) and got nitriles in 53 to 87% yields. It was observed that aldehydes having electron-donating groups e.g. –OH, -NMe_2, -OMe etc. gave higher yields but aldehydes with electron-withdrawing groups required higher temperature and gave lower yields.

Chapter-Ⅲ: One-pot synthesis of 5-substituted-1H-tetrazole from aldehydes catalyzed by $TiCl_3$

Section-A: Chapter Ⅲ (section-A) deals with methodical literature review on tetrazoles,synthesis and its applications.Tetrazole is an important substructure found in many pharmaceuticals.Several methodological works has been done on the synthesis of tetrazoles. The comprehensive literature review states that there is still a necessity of easy and economically favourable method for the synthesis of tetrazoles.

Section-B: Chapter Ⅲ (section-B) deals with Titanium trichloride mediated one-pot transformation of aldehyde (1mmol) (aromatic, aliphatic, heterocyclic) into 5-substituted 1-H tetrazoles , reacting with hydroxylamine hydrochloride (1.2 mmol) and sodium azide (1.5) in DMF under reflux condition.

Preface

The multiple purpose, versatile scope and huse significance of C-Nitrogen bond inspire author to carry out the methodological work on C-N bond forming reaction. As far as medicinal and material properties are concerned, C-N bond has gained a distinctive position in organic chemistry. Most of the pharmaceuticals generally contain C-N bond. Heterocyclic compounds having C-N bond finds immense application in almost all fields of chemistry. Extensive research work has been done to explore the importance of C-N bond, particularly in the area of biological chemistry by synthesizing new class of drugs and the material properties of this class of compounds.

The area describing C-N bond formation reactions has got enormous applications because of wide range of utility in designing the compounds which are of chemical or biological interest. Several new methodologies have so far been developed for the synthesis of these compounds. Most of the methodologies reported are not easy, straight-forward and environmental friendly. The development of mild and green approach of the methodologies is still in progress. Since, there are several kind of compounds having C-N bond, a few methodological work have been dealt with in this thesis. The thesis covered the synthesis of pyrazine derivatives from the reaction of 1, 2-diketone with ethylenediamine under neat reaction condition or on silica-gel at room temperature, synthesis of nitrile from the reaction of aldehydes with hydroxylamine hydrochloride on silica-gel and $TiCl_3$ catalyzed synthesis of 5-substituted 1H-tetrazole.

The principal objective of this thesis is to offer new methodological work of literature on carbon-nitrogen bond formation reaction. The methodologies described in this thesis are cost-effective, mild and environmental friendly which are relevant with the present demand of green and sustainable development.

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Appendix A

List of Published/ Accepted/ Communicated research Papers

1. Clean and Green Approach for One-pot Synthesis of Pyrazine from Ethylenediamine and 1, 2-Diketone or its Analogues under Neat Reaction Condition

   Pranab Ghosh and **Rakesh Ranjan Chakraborty.** *Letters in Organic Chemistry*, **2017**, 14, 566-570.

2. Silica-Gel: An Efficient Catalyst For One-Pot Synthesis of Pyrazines From Ethylenediamine and 1, 2-Diketones or their analogues

   Rakesh Ranjan Chakraborty, Rabindranath Singha and Pranab Ghosh**. Accepted for publication,** *Indian Journal of Heterocyclic Chemistry*.[Ms.ID. # IJHC- 3481-17].

3. One-pot route to nitriles from aldehyde and hydroxylamine hydrochloride on silica-gel.

   Rakesh Ranjan Chakraborty and Pranab Ghosh**.** Asian Journal of Green Chemistry, **2018**, 2, 330-337.

4. $TiCl_3$ catalyzed one-pot protocol for the conversion of aldehydes into 5-substituted 1H-tetrazole

   Rakesh Ranjan Chakraborty and Pranab Ghosh**.** *Communicated toTetrahedron Letters*.[MS. Ref. No: TETL-D-18-01211].

5. Clean and Green Protocol for One-pot Synthesis of Pyrazine from Ethylenediamine and1, 2-Diketone or its Analogues under Neat Reaction Condition

   Rakesh Ranjan Chakraborty and Pranab Ghosh**.** Proceedings of the National Seminar "Frontier in Chemistry 2017" , (September 14, 2017), Department of Chemistry, University of North Bengal, Darjeeling.

Appendix B

List of Poster Presentation/ Participation in the national seminars

1. Clean and Green Approach for One-pot Synthesis of Pyrazine from Ethylenediamine and 1, 2-Diketone or its analogues under Neat Reaction Condition

   Rakesh Ranjan Chakraborty and Pranab Ghosh**. Proceedings of the** National Seminar "Frontier in Chemistry 2017", (September 14, 2017), Department of Chemistry, University of North Bengal, Darjeeling. (Poster presentation).

2. Science Academies Lecture Workshop on "Recent Developments on the Theoretical and Experimental Aspects of advanced Materials"

   September 18-19, 2015 at Department of Chemistry, University of North Bengal

3. Frontiers in Chemistry-2015, UGC and SAP (DRS-Ⅲ). Department of Chemistry, University of North Bengal

Appendix-C

Abbreviations

$TiCl_3$	Titanium trichloride	PE	Petroleum ether
HCN	Hydrogen cyanide	EA	Ethyl acetate
HNO_2	Nitrous acid	NMR	Nuclearmagnetic resonance
$ZnCl_2$	Zinc Chloride	UV	Ultra violet
HCl	Hydrochloric acid	NH_4OAc	Ammonium acetate
TFA	Trifluoroacetic acid	$CHCl_3$	Chloroform
$FeCl_3$	Ferric Chloride	$TMSN_3$	Trimethylsilyl azide
Al_2O_3	Aluminium oxide	$La(OTf)_3$	Lanthanum(Ⅲ) triflate
KCN	Potassium cyanide	TfOH	Triflic acid
CuCN	Cuprous cyanide	KBr	Potassium bromide
$Cu(hfacac)_2$	Copper hexafluoroacetyl-acetonate	THF	Tetrahydrofuran
$InCl_3$	Indium trichloride	NaN_3	Sodium azide
p-TSA	Para toluene sulphonic acid	P_2O_5	Phosphorus pentoxide
t-BuOK	Potassium tertiary butoxide	$AgNO_3$	Silver nitrate
Na_2SO_4	Sodium sulphate anhydrous	$HClO_4$	Perchloric acid
RT	Room temperature	MeOH	Methanol
TLC	Thin layer chromatography	KOH	Potassium hydroxide
FT-IR	Fourier transform infrared spectroscopy	MnO_2	Manganese dioxide
TBAB	Tetra-n-butylammonium bromide	TMS	Tetramethyl Silane
TEA	Triethylamine		
$(NH_4)_2S$	Ammonium sulphide		
[Bmim]Br	1-butyl-3-methylimidazolium bromide		
TBAA	tetrabutylammonium azide		
PFPAT	Pentafluoro phenyl ammonium triflate		
CeO_2	Cerium dioxide		
CH_3CN	Acetonitrile		
$Zn(OTf)_2$	Zinc triflate		
TEMPO	2, 2, 6, 6-tetramethyl piperidine-1-oxyl		
$PhI(OAc)_2$	Iodosobenzenediacetate		
DIH	1, 3-diiodo-5, 5-dimethylhydantoin		
TBAF	Tetra-n-butylammonium fluoride		
PIDA	Phenyliodine (Ⅲ) diacetate		
DMSO	Dimethyl sulfoxide		
DMF	N,N-Dimethylformamide		

General introduction

General introduction

1. A brief introduction of C-N bond

The construction of the C-N bonds of aromatic compounds are particularly important in the field of medicinal chemistry. C-N bond formation reaction is thermodynamically more favourable than C-C bond formation. The construction of C-N bond is of significant importance because it introduces nitrogen atom in organic molecules. Nitrogen containing compounds are extremely important because of their abundance in various natural products and in the synthetic organic compounds that show interesting biological activities. Nitrogen containing organic compounds has gained a considerable amount of attention in synthetic organic chemistry because of its several application in pharmaceutical and agrochemical industries. Beside this, it also plays a role in constructing of naturally occurring biological active compounds like amino acids, naturally occurring heterocyclic compounds, drugs etc. Extensive work has been done on the formation of C-N bond formation and exploring the importance and scope of nitrogen containing compounds. The importance of C-N bond and broad spectrum application of nitrogen containing compounds compels author to carry out the methodological work on carbon-nitrogen bond formation and thereby synthesizing some nitrogen containing compounds.

2. Objectives of the thesis

The C-N bond forming reactions are of great importance because of the enormous application in the field of chemical as well as in biology. There are lot of methodologies in literature which deals with the synthesis of C-N bond forming reaction. Most of the methodologies are not easy, straight-forward and are not environmentally benign. Therefore the development of mild and green methodology is

still required. There are several type of compounds having C-N bond, out of which, a few methodological works are reported in these thesis.The thesis contains the synthesis of pyrazine derivatives from the reaction of ethylenediamine with 1,2-diketone or α-hydroxy ketone or α-bromo ketone under neat reaction condition, synthesis of pyrazines from ethylenediamine and 1, 2-diketone or its analogues catalyzed by silica-gel, synthesis of nitriles from aldehydes and hydroxylamine hydrochloride on silica-gel, synthesis of 5-substituted-1H-tetrazole from aldehydes catalyzed by $TiCl_3$. The unique biological features of these synthesized compounds having C-N bond inspired author to carry out the methodological work in this thesis.

The principal objective of this thesis is to introduce new methodological work for the synthesis of these important compounds by C-N bond forming reactions. The new methodologies presented in this thesis are cost-effective, mild and environmentally benign which meet the requirement under the aspect of green chemistry.

CHAPTER- Ⅰ

One-pot synthesis of pyrazines from ethylenediamine and 1, 2-diketone or its analogues

CHAPTER- Ⅰ

SECTION-A

Ⅰ. A. A brief review on pyrazine, synthesis and its applications

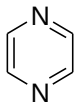
Ⅰ. A.1. Pyrazine

The flavor of food is interesting as well as complicated area of investigation. Severa compounds have been implicated as the key to the flavor of certain foods. During the past few decades, evidences have been made that a class of nitrogen-containing heterocyclic compounds, pyrazines are responsible for the flavor of cooked or roasted foods.[1] 2, 5-dimethylpyrazine is a pyrazine compound which is associated with flavor of potato.[2] Now the question is how these pyrazine compounds are synthesized in food stuffs.Many theories came forward to explain the formation. Carbohydrate degradation in the formation of pyrazine is well documented.[3, 4] There are early reports of isolation of substituted pyrazines from the reaction of ammonia and hexose sugars.[5]

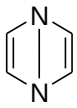
There are theories for the formation of several type of pyrazines. For the simple alkylated pyrazine, Dawes and Edwards in 1966, used model system having fructose and amino acids, isolated 2, 5-dimethyl and trimethyl pyrazine and came to a conclusion that pyrazines are formed in the heated foods by condensation reactions of sugars with amino acids.

Before the elucidation of the structure of pyrazine, pyrazine was known as aldine, paradiazine, and piazine.

Kekule type (1) and Dewar type (2) structure for pyrazine was proposed and supported by various group,[6] but Kekule structure was selected finally after a study of molecular refraction of a few pyrazine derivatives by Bruhl[7]

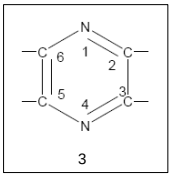


1



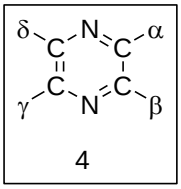
2

The nomenclature of pyrazines was even difficult because of the fact that early workers were in confusion regarding the structure of pyrazine. 2, 5-dimethylpyrazine was thought to be the parent compound of the class and was given the generic name“ ketine.”Following the ring index, [8] the numbering of pyrazine was derived and the numbering is as follows-



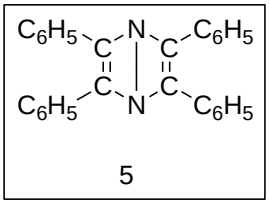
3

An alternative scheme was used by T.Tictor and V. Richter in his *Lehrbuch der organischen Chemie*



4

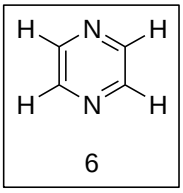
Historically the structure elucidation of pyrazine derivative was first made by japp and Wilson and later by Pauling Japp and Wilson[9]. They started determining the true nature of benzoinimide and renamed it as ditolanazotide. Finally Japp and Burton [10] decided that the compound was azine and assigned its structure with the name “ tetraphenylazine.”



5

Snape and Brooke published a paper[11-12] in 1897 in which they revealed that amarone, ditolanazotide, benzoinimide and tetraphenylazine are the same substance that is tetraphenylpyrazine. There was still remained a doubt about the exact location of the double bond in pyrazine molecule. Bruhl finally established the structure 1 after study on molecular refraction of a lot of pyrazine derivatives.

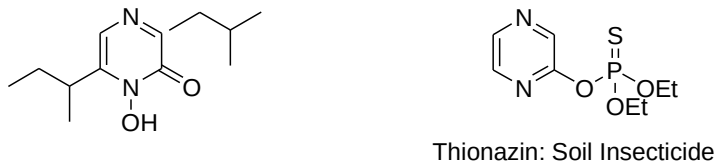
Pyrazine is an aromatic heterocyclic compound with molecular formula $C_4H_4N_2$. It is a symmetrical molecule having point group D_2h.



6

Figure. Ⅰ.A.6. Finally accepted structure of pyrazine

Pyrazines are a priviledged class of N-heterocyclic moieties, which have numerous applications in pharmaceutical as well as in agrochemical.[13] (Fig. Ⅰ.A.7)



Aspergillic acid: Fungal Antibiotics

Thionazin: Soil Insecticide

7

Fig. Ⅰ.A.7. Biologically important pyrazine derivatives

Pyrazines belong to important class of aroma fragrances,[14] and potential pharmacophore of a lot of biologically active substances.[15] Pyrazinamide acts against Mycobacterium tuberculosis and used for tuberculosis treatment.[16]

A bis-steroidal marine natural product Cephalostatin have a pyrazine core, which induces apoptosis with no prerequisite of an active caspase-8 and apoptosome formation.[17]

Because of these varied applications with pyrazine moieties, their synthesis has always been the goal of many research group.

Ⅰ.A.2. Natural Occurance

Pyrazines are widely distributed in nature. They occur naturally and are anthropogenic. Alkylated pyrazines are most abundant in nature. Pyrazines are found in plants, animals and micro-organisms (Woolfson and Rothschild, 1990; Beck et al., 2003). In plants, they are found in leaves, seeds, spices, fruits, vegetable oil and vegetable tissues (Table. Ⅰ.A.1.). Pomerine ants, the first insects in which pyrazines were found (genus Odontomachus), where they acts as alarming pheromones (Wheeler and Blum, 1973). Their occurrence in bees, flies, wasps, butterflies, moths, aposematic beetles and grasshopper was reported (Table. Ⅰ.A.2.). Pyrazines impart aromas in food (Table. Ⅰ.A.3.). Dimethyl and trimethylpyrazines impart aroma of the roasted nuts and coffee respectively (Rowe, 2005).Generaly alkylated pyrazines are synthesized by few bacterial and fungal species. Aspergillic acid was the first natural product shown to be cyclic hydroxamic acid (Micetich and Mac Donald, 1965), synthesized by Aspergillus flavus.3, 6-diisobutyl-2-pyrazinone (flavacol),

neohydroxyaspergillic acid, muta-aspergillic acid and 2-hydroxy-3,6-di-sec-butylpyrazine (Buchanan and Houston, 1982) are other derivatives of aspergillic acid. Paenibacillus polymyxa (Beck et al, 2003) (Table 6) produces dialkyl mixtures of isobutyl and sec-butyl moiety. Pyrazines having potato

like odour are produced by species of Enterobacteriaceae family (Gallois and Grimont, 1985). 2, 3, 5-trimethylpyrazine, 2,5-Dimethylpyrazine, 2-methyl-5-isopropylpyrazines are synthesized by Klebsiella pneumonia, Citrobacter freundii and Enterobacter agglomerans, are attractive to the Mexican fruit fly, Anastrepha ludens (Robacker et al, 2002).

Table . Ⅰ .A.1. Occurance of pyrazines from plants

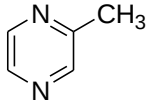
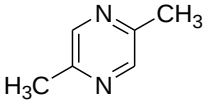
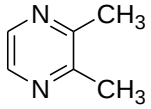
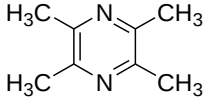
Pyrazines	Source	References
2,5-Dimethylpyrazine 2,3,5Trimethylpyrazine 2,5-Diethylpyrazine	Fusel Oil	Cheesman, 1972
Alkylpyrazines	Commercial peanut butter preparation	Joo et al, 1997
2,3-Dimethylpyrazine 2-methylpyrazine 2,3,5Trimethylpyrazine	Chitin pyrolysis at 300-500^{0}C	Knorr et al, 2006

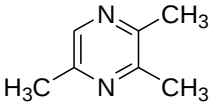
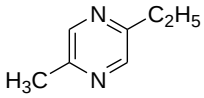
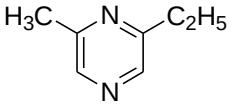
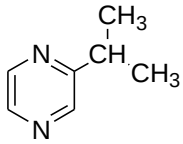
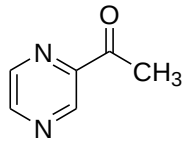
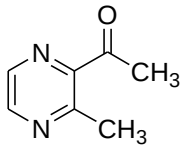
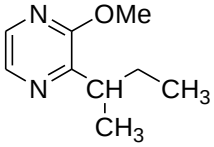
Table. Ⅰ.A. 2. Occurance of pyrazines in animals

Pyrazines	Occurance	References
Pyrazines	Odontomachus hastatus Odontomachus	Wheeler and Blum, 1973
Pyrazine derivative	Faecal pellets of male rabbits and scent glands of Canadian *beaver*	Woolfson and Rothschild, 1990
Pyrazine derivatives	Ants, flies, wasps, bees, species of aposematic beetles,moths, butterflies, plant bugs, grasshoppers	Moore *et al.*, 1990
Pyrazine derivative	Urine of coyotes and man	Albone *et al.*, 1984; Woolfson and Rothschild, 1990
Pyrazine-luciferin	Coelenterates, squids, fishes and ostracods	Mc Capra, 1982; Herring *et al.*, 1982

Pyrazine derivative	Nasal mucosa of cow and rabbits, gular glands of crocodiles, and alligators	Weldon and Sampson, 1988

Table. Ⅰ.A. 3. Occurance of pyrazine in food

Pyrazine	Occurance	Odour
	Baked fried and roasted products	Musty, nutty roasted cocoa like
	In many food flavours, dairy, vegetable, meat and roasted products	Roasted, cocoa like
	Vegetables, meat, dairy, roasted Products, coffee, cocoa, potato chips, papaya, shrimp, asparagus, fried potato and cabbage	Roasted meat, vanilla and chocolate like
	In many flavours, bread, brandy, beef, rum, whisky, cocoa and coffee	Musty nutty and burnt flavour

	Nuts, meat, roasted products, Whisky, rum and popcorn	Burnt, earthy, roasted, and tobacco like
	In many flavours, bread,vegetables, meat, whisky, coffee and cocoa	Roasted coffee and cocoa like
	In many food flavours, meat, fish, roasted products and in beverages of alcohol	Roasted cocoa and coffee connotations
	In fried chicken, peanut cocoa filbert,	Dusty roasted nuts
	In roasted flavours, bread, cocoa, popcorn, peanut, filbert	Pop corn, nutty, bread crust
	In meat, coffee, cocoa, and fried potato	Roasted potatoes, cereals and nutty vegetable
	In green bell pepper, pathegrain oil	Pea green, earthy and galbanum

Ⅰ.A.3. Structure of pyrazine

Pyrazine is represented as a resonance hybrid of the following canonical structures. The molecule is planar. Pyrazine is stabilized by about 40 kcal/mol as in pyridine and benzene.

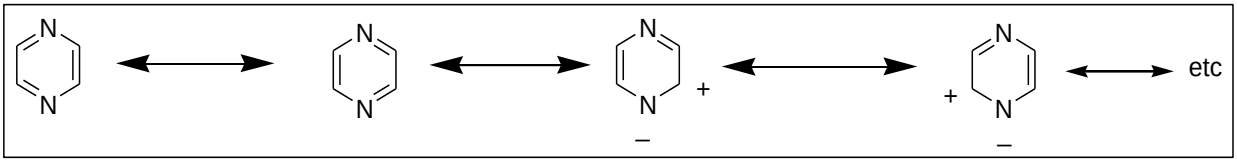


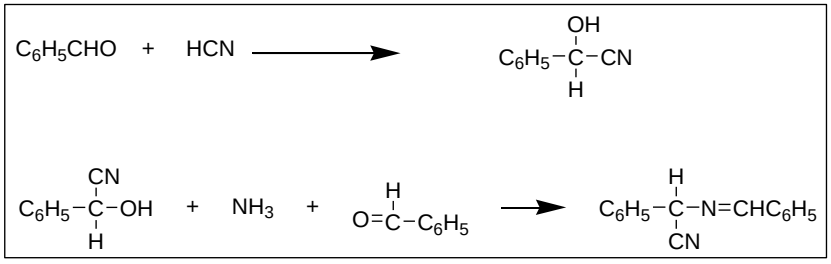
Fig. Ⅰ.A.8. Resonance structures of pyrazine

Ⅰ.A.4. Application of pyrazines

Pyrazines have wide application in pharmaceutical, agrochemical and industrial field. Pyrazines impart flavor to different food stuff. Pyrazines are widely used in medicine as diuretics, antineoplastics, anti-inflammatory, antidepressants, antituberculosis and acts as bactericides, fungicides and plant growth regulators. Pyrazines also play an important role in making chiral heterocyclic ligand in coordination chemistry.[18]

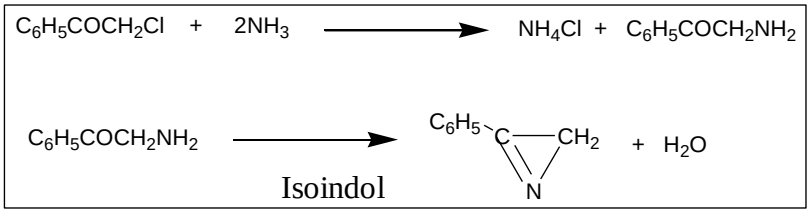
Ⅰ.A.5. Method for the synthesis of pyrazine

The procedure for the synthesis of pyrazine was first published by Laurent in 1844.[19] Starting from benzaldehyde containing some hydrogen cyanide, crude benzaldehyde, with ammonia and obtained " benzoyl azotid". Actually the compound was α-benzalaminophenylacetonitrile:



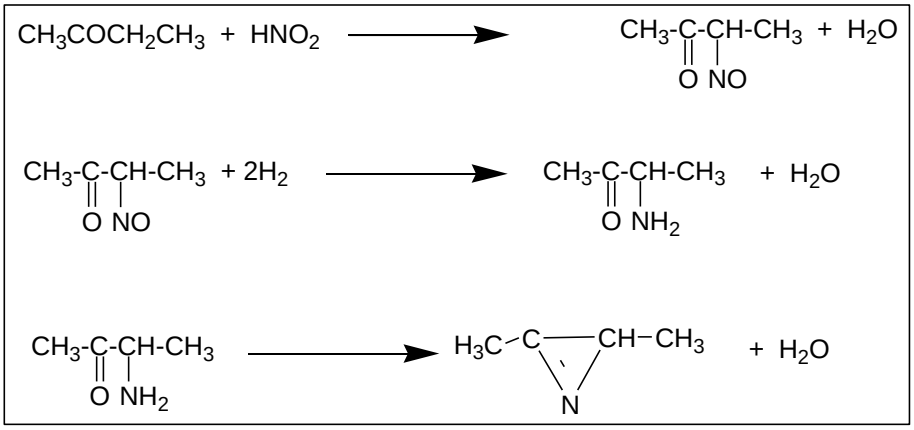
Scheme. Ⅰ.A. 1. Synthesis of α-benzalaminophenylacetonitrile

Then, he destructively distilled "benzoylazotid"and isolated aproduct, called amarone. After twenty one years, Erdmann.[20] obtained an apparently new substance, benzoinimide, which is obtained by the action of ammonia on benzoin. Stadel and Rugheimer[21] published a new paper , where he described the formation of a compound called, isoindol. The reaction was performed by the action of ammonia on ε-chloroacetophenone. According to them, isoindol was inner anhydride of amino ketone and was formed as follows:



Scheme. Ⅰ .A. 2. Synthesis of isoindol

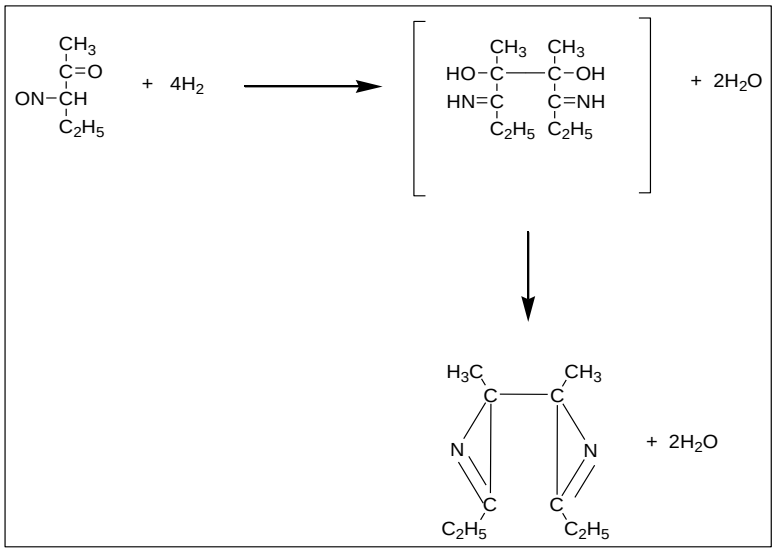
This compound represented the first inatance of a structural formula for pyrazine. In 1881, Etard[22] obseved a new compound, glycolin, that could be isolated from the distillate, resulted from heating a mixture of ammonium salt and glycerol. But Victor Meyer already elucidated the nature of this compound at Zurich. Meyer was also interested in nitroso derivatives. Gutknecht was assigned to reduce the product from the action of nitrous acid on ethyl methyl ketone. Now it is known that this product was oxime. But then the compound was thought to be true nitroso compound. They concluded that an inner anhydride of amino ketone was formed by reduction.



Scheme. Ⅰ.A. 3. Synthesis of substituted isoindol

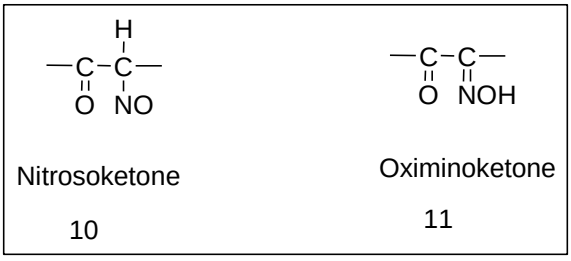
After a lot of analysis, Gutknecht thought that the compound might contain one hydrogen atom less that was indicated by the formula. Finally F. P. Treadwell.[23] clarified the point in 1881. He reduced" nitrosoethylacetone" and isolated a crystalline hydrate. After keeping the crystal in desiccators, he obtained anhydrous oil. Analysis of the oil proved to contain one hydrogen atom less than that anticipated from the formula of "inner anhydride" of amino ketone. Further vapour-density indicated that the molecular weight was twice than expected for the compound.

Using the model, reduction of acetone to pinacol, Treadwell assumed that the reaction is preceded as follows:

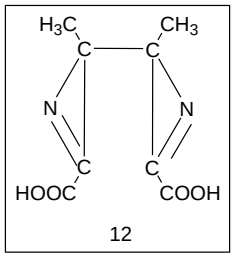


Scheme. Ⅰ.A. 4. Synthesis of nitrosoethylacetone

This new series of nitrogenous compound was known as "ketine" to distinguish from ketones. According to Treadwell theory, the simplest member is obtained from acetone. The other members were regarded as derivatives of ketine. Thereafter, V. Meyer published a paper[24] in which he suggested that since the product obtained from the action of nitrous acid on ketones, it would be failed to respond Liebermann test of nitroso group, the compound was not nitroso compound but rather isomeric oximes:



After comparing the reduced product of nitro-amine and ketone-pinacol, he discarded the Treadwell theory. The first conception of ketenes as ring compound was introduced by Wleugel[25] , who was concerned with the reduction of nitrosoacetoacetic ester. Thus this was obtained as



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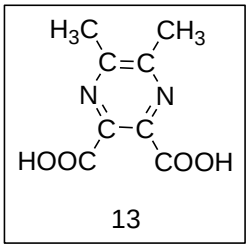
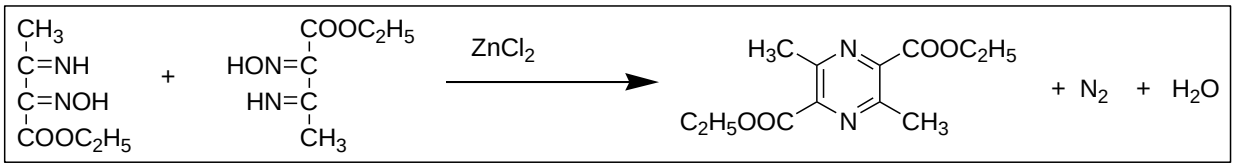
Utilizing the C-C bonds involved in the inner anhydride ring, he closed the six-membered ring as follows:



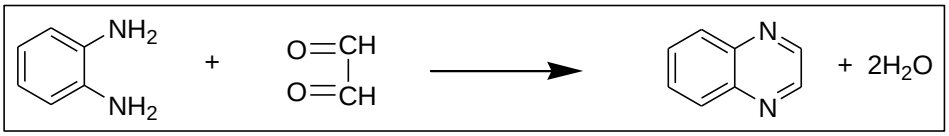
13

This led to the formulation of a heterocycle, which according to Wleugel, conceived to be pyridine, where CH group para to nitrogen was replaced by another nitrogen atom. This is the modern concept of pyrazine nucleus. But there remained a defect in derivation, since Wleugel had utilized the ketine (pinacol) mechanism. L. Oeconomides in 1886[26] demonstrated that this mechanism was obsolete. He tried to dehydrate Wleugel's diacid to acid anhydride, a reaction which clearly shows that the two carboxyl group were ortho to one another. But the reaction was failed and the conclusion was that the functional groups were assigned at wrong position rather the actual position of the carboxyl groups were in para, the experiment is as follows: Iminoisonitrosobutyric ester was heated with molten zinc chloride, a reaction mechanism to yield a" ketine" indicating that the carboxyl group must be in para position:



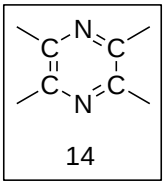
Scheme. Ⅰ.A. 5 . Oeconomides's Synthesis of pyrazine derivative

Hinsberg[27] further synthesized quinoxaline, a condensed pyrazine, from glyoxal andortho-phenylenediamine:



Scheme. Ⅰ.A. 6. Hinsberg's method for the synthesis of benzopyrazine

Thus, the structure of ketine nucleus was established as



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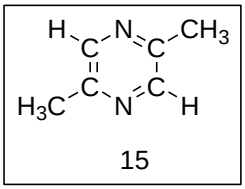
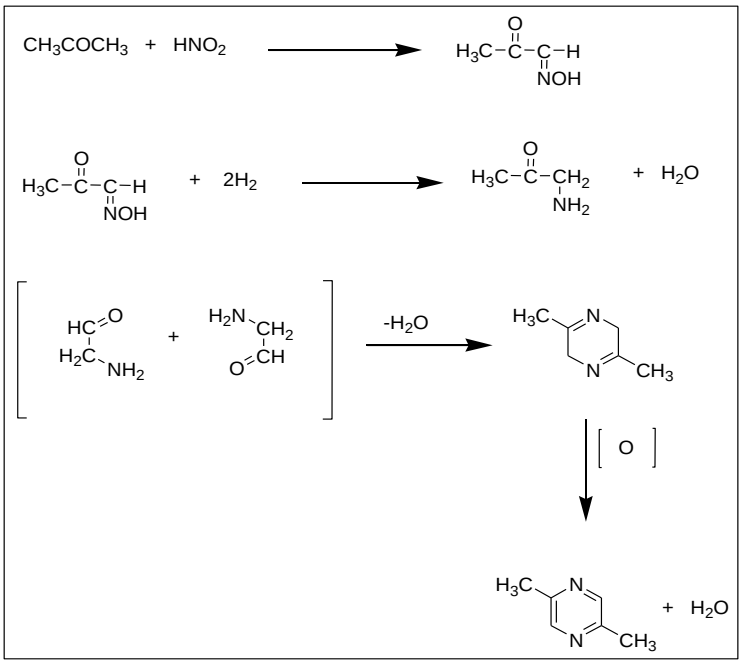
And ketine, that was thought to be simplest member, infact was dimethyl derivative.



15

Mason [28] and Wolff [29] independently suggested the name pyrazine in order to correlate with pyridine. Wolff acknowledged that the mechanism put forth by Meyer , that gave rise to pyrazine by reduction of isonitroso ketone had an intermediate amino ketone which condensed with it immediately to yield dihydropyrazine that was oxidized to the expected pyrazine. Thus, starting with acetone:



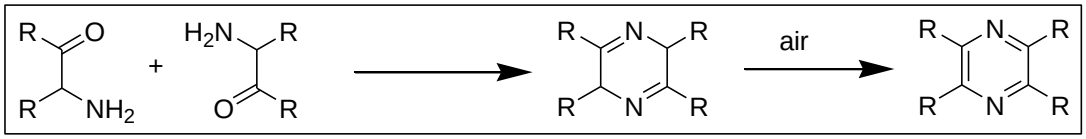
Scheme. Ⅰ.A. 7. Mason's synthesis of pyrazine

V. Meyer [30] was not in agreement with the term" pyrazine" since Knorr[31] had already used the term for pyrazole tetrahydride. He rather proposed the generic name "aldine," because the simplest member resulted from self-condensation of the hypothetical aminoacetaldehyde.

With a systematic nomenclature, Wildman[32] finally resolved the issues. He named azines for those compounds which had a six-membered ring having nitrogen and carbon atoms. Therefore, compounds having two nitrogen atoms in the ring were named as diazines. These were further classified as ortho, meta or para diazines according to the relative position of two nitrogen atoms. Mason condensed these names into oiazines, miazines and piazines respectively. The results of the early workers were finally clarified in the light of newly elucidated structures of pyrazines.

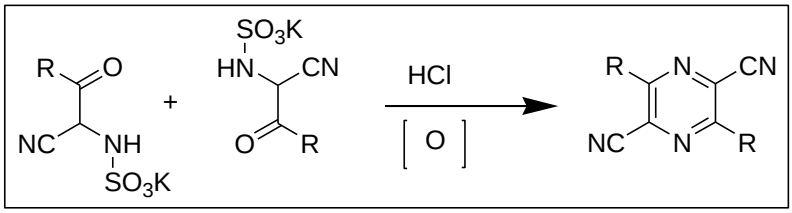
Historically simple pyrazine was synthesized as early as in 1876 by Stacdel-Rugheimer.[33] In this method, 2-chloroacetophenone was reacted with ammonia to form amino ketone, this got condensed and oxidized to pyrazine. In 1879 Gutknecth modified the method a little. This method was also self-

condensation but differ in the synthesis of alfa-ketoamine, the chlorine compound here is a lachrymatory agent[34]



Scheme. Ⅰ.A. 8. Gutknecth's method for synthesis of pyrazine

At the beginning of the twentieth century, Gastaldi synthesized pyrazine in a very easy way.[35]



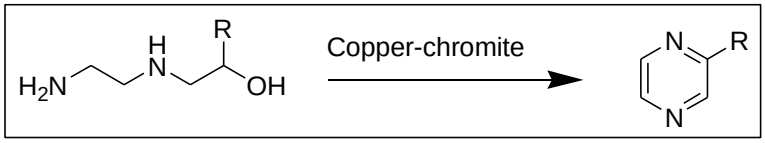
Scheme. Ⅰ.A. 9. Gastaldi's method for synthesis of pyrazine

Gastaldi's methodology has drawn attention to synthetic organic chemists for many years. It served a good method for incorporation of nitrile group into heterocyclic moiety. Among several developed methods, pyrazines are synthesized by the reaction of diols with diamines in vapour phase condition in presence of granular alumina.[36] Catalytic systems such as copper-zinc-chromium,[37] copper-chromium,[38] zinc-phosphoric acid-manganese,[39] and silver,[40] are patented as a catalyst for the synthesis of 2-methylpyrazine from propylene glycol and ethylenediamine. Pyrazines are also formed by catalytic dehydrogenation of ethanolamine vapour. The catalysts in these case are zinc oxide, copper oxide, copper and sodium carbonate.[41] Pd-catalyzed cross-coupling reaction and condensation of α-amino ketone also produced pyrazine derivatives.[42-43] Pyrazines were synthesized by condensation of epoxides with diamines using copper-chromium catalyst.[44]

Zhang et al. (2001) used 2, 2-diethoxyacetophenone to react with 2, 3-diamino-3-phenylthio-acrylonitrile to yield 6-phenyl-3-phenylthio-pyrazinecarbonitrile (scheme 10) in good yield in the presence of excess trifluoroacetic acid (TFA).

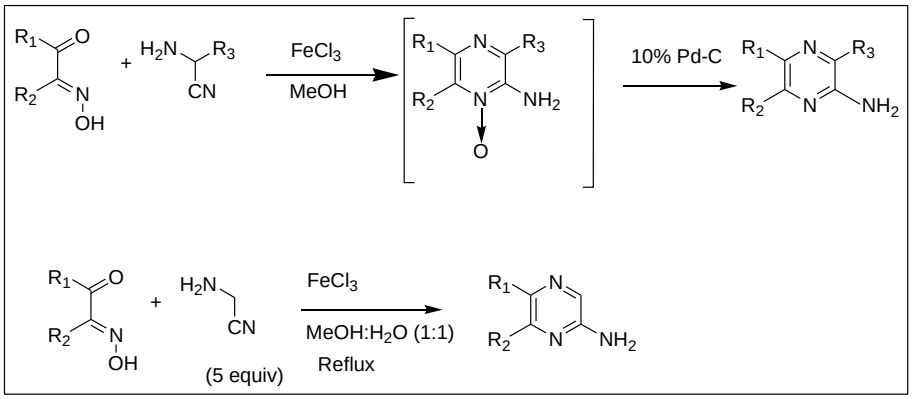
Scheme. Ⅰ.A.10.Reaction of 2, 3-diamino-3-phenylthioacrylonitrile with 2, 2-diethoxyacetophenone.

Lee et al. in 1990, patented (U.S. Patent No. 4, 966, 970, 1990) the formation of pyrazine by copper-chromite catalyst (Scheme 11). The reaction was said to produce up to 97% yield.



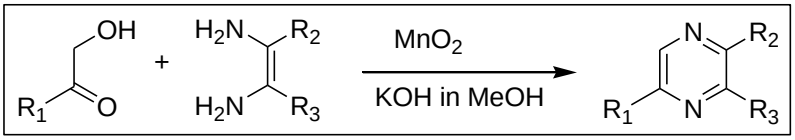
Scheme. Ⅰ.A. 11. Synthesis of pyrazine by copper chromite

Itoh et al. in 2002 reported the synthesis of pyrazine by $FeCl_3$ as a catalyst. Isonitroso-acetophenone was reacted with aminoacetonitrile in presence of one equivalent $FeCl_3$ to produce N-oxide pyrazine and then hydrogenation with 10% Pd-C to yield pyrazine (Scheme 12). One step reaction between isonitrosoacetophenone and five equivalents of aminoacetonitrile catalyzed by $FeCl_3$ is a straight forward preparation producing better yield of pyrazine.



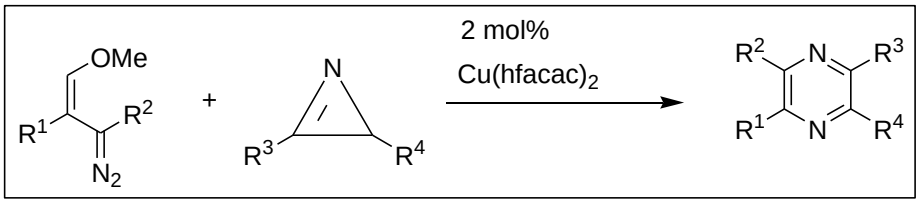
Scheme. Ⅰ.A. 12. Synthesis of pyrazine by $FeCl_3$

After one year, Richard (2003) reported the synthesis of pyrazine using excess of manganese dioxide (Scheme 13). In this reaction, α-hydroxylketones were made to react with 1, 2-diaminoalkene in presence of manganese dioxide. Methanolic KOH was added to the reaction mixture to afford excellent yield.



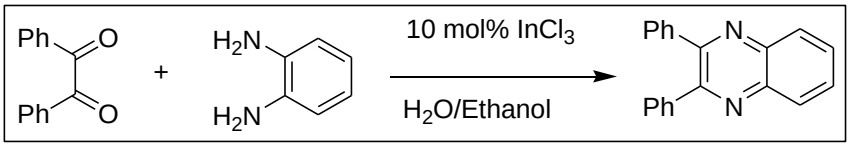
Scheme. Ⅰ.A. 13. Catalytic formation of pyrazine by Richard

Synthesis of unsymmetrically substituted pyrazine has always been challenge to organic chemist. N.S.Y. Loy, S. Kim and C-M. Park[45] in 2015, reported a reaction (Scheme 14) in which, α-imino carbenoids derived from α-diazo oxime ethers was exploited for synthesis of pyrazine, where α-diazo oxime ethers reacts with 2H-azirines producing highly substituted pyrazine derivatives.



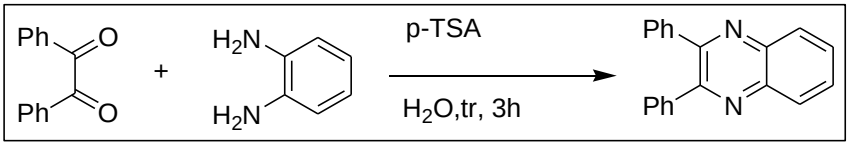
Scheme. Ⅰ.A. 14. Synthesis of pyrazine by 2H-azirines with α-diazo oxime ethers by N.S.Y. Loy et al (2015)

Hazarika et al. reported an environmental friendly methodology for the synthesis of quinoxaline, a benzopyrazine (scheme 15) in 2007. In this reaction, 1, 2-diketone reacts with o-phenylenediamine in presence of 10 mol% indium chloride in aqueous solution at room temperature.



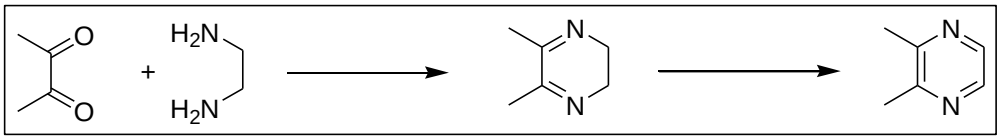
Scheme. Ⅰ.A. 15. Synthesis of benzopyrazine by Hazarika et.al (2007)

Mahadik et. al in 2014 used ultrasonic wave technique for the synthesis of quinoxaline, a pyrazine derivatives, from the reaction of benzil and o-phenylenediamine in presence of p-toluenesulfonic acid (p-TSA) (scheme 16). The advantage of this reaction was, shorter reaction time, less generation of toxic products, milder reaction condition and higher yield.



Scheme. Ⅰ.A. 16. Synthesis of quinoxaline by Mahadik et.al (2014)

So far the synthesis of pyrazine is concerned, direct condensation reaction of 1, 2-diamine with 1, 2-diketones is the acceptable and classical way for the synthesis of pyrazine via intermediate named dihydropyrazine.

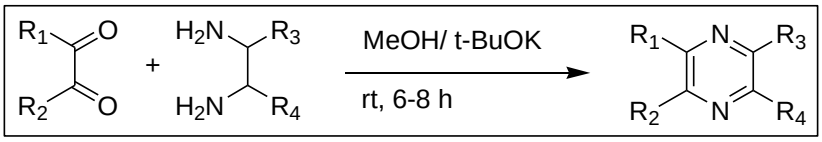


Scheme. Ⅰ.A. 17. Straight forward synthesis of pyrazine

Green approach in synthesizing pyrazine

Pyrazine is synthesized from several reaction methods, but most of the reaction suffer from drawbacks, such as, poor yield of reaction, longer reaction time, use of toxic solvents and metals, and tedious work-up processes.[46] In modern era, where green chemistry is emerging as most vital, eco-friendly methodology for synthesizing pyrazine has been developed. In this context, Ghosh and Mandal (2012)[47] successfully developed an eco-friendly protocol for synthesizing pyrazine (Scheme 18). This protocol involves a simple condensation of 1, 2-diketone with 1, 2-diamine in presence of

potassium tert-butoxide to obtain 72-88% of pyrazine at room temperature. The reaction was supposed to proceed via the formation of dihydropyrazine followed by aromatization to produce pyrazine.



Scheme. Ⅰ.A. 18. Green approach for synthesis of pyrazine by Ghosh and Mandal (2012).

Ⅰ.A.6. Conclusion

Green chemistry or sustainable chemistry, is a philosophy of chemical research that develops the chemical transformation, that minimizes the use and generation of hazardous products. Green chemistry is devoted to reduce pollution in atmosphere. Pollution Prevention Act in 1990, in the united states, focused on minimizing the hazard and maximizing on efficiency of chemical choice. This law states that:

. the design of methods to maximize the amount of raw material that ends up in the product

. the use of safe, environment-friendly substances, including solvents, whenever possible

. the design of energy efficient processes

. the best form of waste disposal, not to create it in the first place.

An organic synthetic protocol, from green chemical point of view, should have the above criteria. All the existing synthetic methodologies for the synthesis of pyrazines are useful, but all of them suffer from a number of drawbacks if we consider from green chemical point of view. Therefore,

development of mild, environmentally benign and efficient method for synthesizing pyrazines and to keep the green chemistry principles in mind is a major challenge in organic synthesis.

Ⅰ.A.7. References

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CHAPTER-Ⅰ

SECTION-B

One-pot synthesis of pyrazines from Ethylenediamine and 1, 2-diketone or its analogues under neat reaction condition

Ⅰ.B. Present Investigation

Ⅰ.B.1. Background of the present investigation

Heterocyclic compounds are omnipresent in nature [1]. Among different N-heterocyclic compounds, pyrazine and its congeners have broad spectrum of biological activities[2] such as anticancer, antituberculosis [3], antimicobacterial activity, antimalarial, antiHIV and cytotoxicity [4]. In addition, these heterocycles are widely applied to other industrial fields, for example,in the preparation of perfumes, pharmaceuticals, agricultural chemicals [5]. It also plays an important role in making flavor ingredient in food and pheromones in various insect [6].It is a versatile synthetic intermediates [7]. Owing to vast and outstanding applications, several synthetic strategies have been developed for their synthesis over the years [8]. Among several methods developed, pyrazines are formed by catalytic dehydrogenation of the vapour of ethanolamine.The catalysts used were copper oxide, zinc oxide, copper, sodium carbonate[9]. Condensation of α-amino ketone[10], Pd-catalysed cross coupling reaction also produced pyrazine derivatives [11]. Further, pyrazine compounds were prepared by the reaction of diamine with diol in vapour phase, catalysed by granular alumina [12]. Catalytic system such as copper-zinc-chromium [13], zinc-phosphoric acid-manganese [14], copper-chromium [15] and silver [16] were also used for the preparation of 2-methyl pyrazine from propyleneglycol and ethylenediamine. Pyrazines were synthesized from the condensation of epoxides and diamines using copper-chromium catalyst [17]. Piperazines gets dehydrogenated in the presence of palladium catalyst

to produce pyrazines in high yield[18]. A-hydroxy ketones and 1, 2-diamine also produce pyrazines via MnO_2 catalyzed tandem oxidation reaction under refluxing conditions, but the yields were not so encouraging [19], moreover this reaction requires an excess amount of MnO_2 catalyst that detracts from the commercial point of view and green condition [20]. Direct condensation of 1, 2-diketones with 1, 2-diamine has so far been the better procedure of pyrazine synthesis through dihydropyrazine [21]. Although, there are several methods of pyrazine synthesis in literature, most of them are regarded as ineffective because of poor yield, long reaction time, tedious work-up process and drastic reaction condition [22]. Although, a few of them are apparently successful, but a convenient and milder laboratory procedures for dehydrogenation were unsuccessful and most of the methods are limited by long reaction time, use and generation of hazardous substances and heavy metals as the catalyst [23].Therefore development of efficient, mild and environmental friendly method for pyrazine synthesis has been a long cherished goal for organic chemists.

Recently, environmentally-friendly reaction processes have been extensively studied from the view point of green chemistry. Solid acid catalyst under heterogeneous condition [24] plays an important role in organic synthesis. Generaly solid acid catalysts are clay and silica based[25] .But these type of reaction requires an appreciable amount of solvent in work-up process [26]. The concept of neat reaction is consistent with the dream of green chemistry in true sence. Neat reaction is a solvent-free methodology where a mixture of reactants are grinded in absence of any solvent.The easy work-up and devoid of any solvent makes it justified from the stand point of green chemistry.

The primary demands of green synthesis include minimization of steps which involves one-pot tandem reactions as well as catalytic processes under metal-free conditions [27]. Since there is no

method developed for the one-pot and metal-free tandem synthesis of pyrazines from ethylenediamine with 1,2-dicarbonyl compounds or analogues, we were interested to develop an alternative solvent and metal-free greener process for the synthesis of pyrazines directly from ethylenediamine with 1,2-dicarbonyl compounds or with analogues at room temperature.In recent days , solvent-free synthesis have attracted the attention of chemists because they are environmentally benign processes. In continuation of our interest in the development of solvent-free synthesis [28], herein we report a new synthetic strategy for the preparation of pyrazine derivatives from ethylenediamine with 1, 2-diketone or with analogues under neat reaction condition.

In connection with our present interest , we explored the synthesis of pyrazines through the metal-free, solvent-free tandem condensation in one-pot protocol.

Ⅰ.B.2. Result and discussion

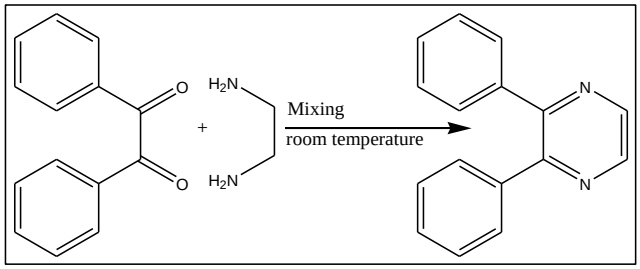
We report herein our findings that finally established a practical and clean procedure for the synthesis of pyrazines derivatives directly from ethylenediamine with 1, 2-diketone or with analogues via one-pot condensation reaction under metal-free condition at room temperature.There was no other by-product detected by analysis of the crude product,the conversion was high and the isolation of the desired pyrazine was achieved in excellent yield.A large variation of functional groups attached with the aromatic ring of 1, 2-diketones was observed with excellent conversions to pyrazines derivatives.

Our studies began with the reaction of ethylenediamine and benzil under neat reaction condition.We set-up the reaction by adding the reacting components i.e mixture of ethylenediamine (1mmol) and benzil (1mmol) mixture into a glass plate and stirred with a glass rod at room temperature and left for 10 hrs. The reaction mixture was then extracted with ethylacetate and washed several times by water and the extract was filtered through anhydrous Na_2SO_4. Finally 56% 2, 3-diphenyl pyrazine (**entry 2, Table.B. 1**) along with unreacted benzil were separated by column chromatography over

silica-gel (60-120 mesh) where pet-ether and ethylacetate mixture was eluent. Thereafter we used mortar for grinding the reaction mixture for a few minutes and transferred the mixture into a 50 ml round-bottom glass bottle and it was kept under magnetic stirrer for better result. We raised the reaction temperature upto 100∘C (**Table.1.B.1. entry 1**) and found no product. We used mono ketone (acetophenone) with ethylenediamine but the reaction was unsuccessful.

Encouraged by the model reaction with benzil and ethylenediamine on neat reaction condition, several experiments regarding time and proportion optimization were carried out for the newly developed general protocol for the synthesis of pyrazine derivatives (Table.1.B.1 and Table.1.B.2). Finally we could optimize the reaction condition as benzil (1mmol) and ethylenediamine (2mmol) mixture was kept on magnetic stirrer for 6 hrs and got 2, 3-diphenyl pyrazine (77%) as a sole product (**entry 3, Table.1.B.1**).

In order to show the general applicability, we attempted the recent procedure to a number of chemically diversified ketone and ethylenediamine to synthesize pyrazine derivative (**Table. Ⅰ.B.3**) and obtained the identical result in each case.In the present investigation, it is found that no additional steps required to aromatize the dihydropyrazine derivatives as reported in the early methods which are the main advantage of this procedure (**scheme. Ⅰ.B.1**).



Scheme. Ⅰ.B.1. One- pot condensation of ethylenediamine with 1, 2-diketone or with analogues resulting pyrazines.

Table. Ⅰ.B.1.Optimization of time(h) for one-pot condensation of ethylenediamine (1mmol) with benzil (1mmol).

Entry	Temp (^{0}C)	Time (h)	Conversion(%)[a]
1	100	12	Nil
2	RT	10	56
3	**RT**	**6**	**77**[b]
4	RT	8	42
5	RT	1	38
6	RT	2	34
7	RT	0.5	25

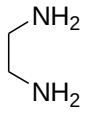
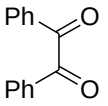
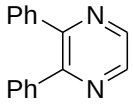
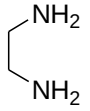
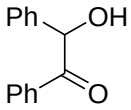
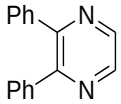
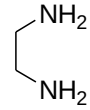
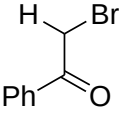
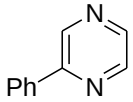
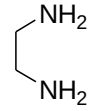
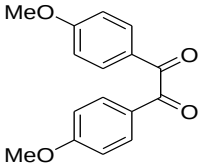
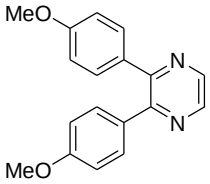
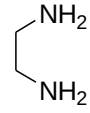
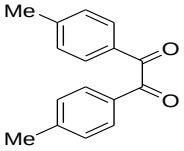
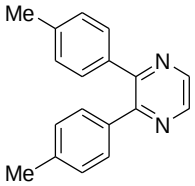
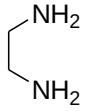
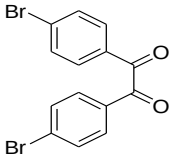
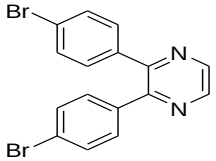
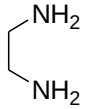
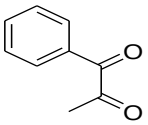
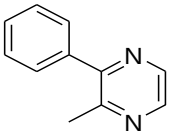
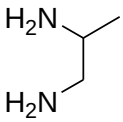
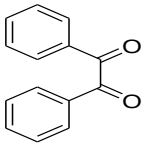
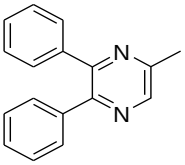
[a]Isolated yield.; [b]Optimized reaction condition.

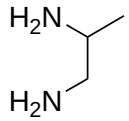
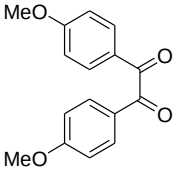
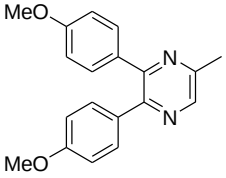
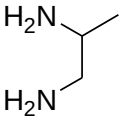
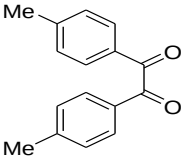
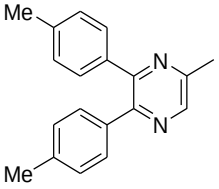
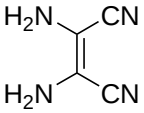
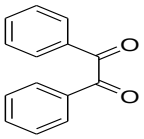
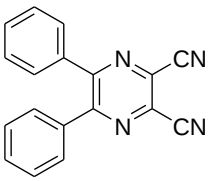
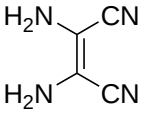
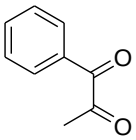
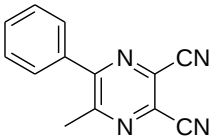
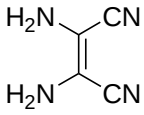
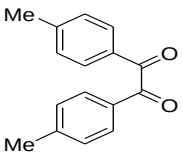
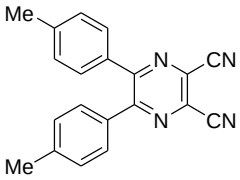
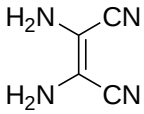
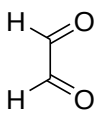
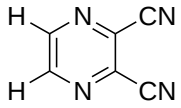
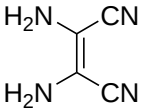
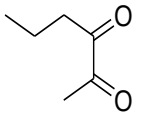
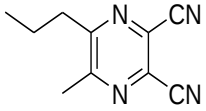
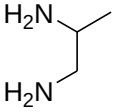
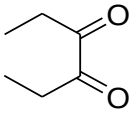
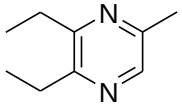
Table. Ⅰ.B.2. Optimization of proportion of ethylenediamine (mmol) with benzil (mmol)

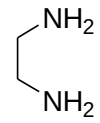
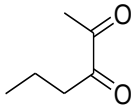
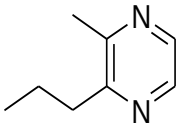
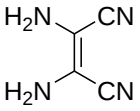
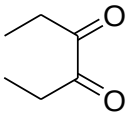
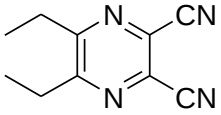
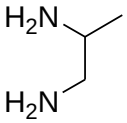
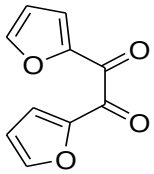
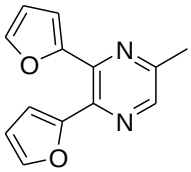
Entry	Ethylenediamine (mmol)	Benzil(mmol)	Conversion(%)[a]
1	1	1	52
2	1	0.5	54
3	**2**	**1**	**77**[b]
4	1.5	1	72
5	0.5	1	51
6	2.5	1	68

[a]Isolated yield; [b]Optimized condition

Table. Ⅰ.B.3. Condensation of ethylenediamine with 1, 2-dicarbonyl compounds or with α-hydroxy ketones or with α-bromo ketone at room temperature

Entry no	Ethylenediamine	1,2-dicarbonyl compound/ analogues	Time(h)	Product	Yield(%)
1			6		77
2			6		75
3			6		68
4			10		76
5			8		81
6			7		80
7			6.5		75
8			5		73

9			5.5		73
10			6		85
11			5		85
12			7		86
13			6		75
14			6.5		82
15			5.5		75
16			7		73

17			8		76
18			7		72
19			5.5		81

Note:% Yield refers to the isolated yield of all compounds.

With the optimized condition (as in Table. Ⅰ.B.1, entry 3), we examined its practical application with a variety of 1, 2-diketone derivatives or with analogues. The result are presented in Table. Ⅰ.B. 2. It can be seen that different keto compounds undergo one-pot condensation with ethylenediamine and gave rise to the formation of corresponding pyrazines in excellent yields.

Ⅰ.B.3. Experimental

Ⅰ.B.3.1. Reaction procedure and purification

1 mmol of recrystallised benzil and 2 mmol of ethylenediamine were added to a mortar. The mixture was grinded for a few minutes and transferred to a 50 ml round bottom flask and was kept stirring with a magnetic spinning bar for 6 hrs. The reaction checked by TLC (ethylacetate and pet-ether). The product was extracted by ethylacetate, washed by water and filtered through anhydrous Na_2SO_4. Product was purified by column chromatography using silica-gel (60-120 mesh). Petroleum ether-

Ethylacetate (PE-EA) mixture were used as eluent. All the products were characterized by IR, ^{1}H NMR and ^{13}C NMR.

Ⅰ.B.3.2. Spectroscopic measurement

UV spectra were recorded in JASCO V-530 UV/VIS Spectrophotometer, IR was recorded in Perkin-Elmer FT-IR Spectrophotometer; NMR was recorded in Bruker Advance 300 MHz FT-NMR instrument using TMS as the internal standard. NMR spectra were recorded in $CDCl_3$. The chemicals used were purchased from Merck, Thomas-Baker and were used as received. No further purification was done.

Ⅰ.B.4. CONCLUSION

In conclusion, we have explored a solvent and metal catalyst free, one-pot facile synthesis of pyrazine derivatives from ethylenediamine (2mmol) and 1, 2-diketone or with α-bromo and α-hydroxy ketone (1mmol) under neat reaction condition at room temperature. Advantages of this protocol are, avoiding harmful organic solvent which causes environmental pollution, excellent yield and easy work-up process**.** the present work demonstrates the synthesis of bio-active scaffold pyrazine derivatives directly from ethylenediamine and 1,2-diketone or with its analogues via one-pot condensation reactions under neat reaction condition at room temperature.The conditions are straightforward, mild, eco-friendly and no other side-products are obtained.Green process of preparation of pyrazines from ethylenediamine and keto-compounds is developed that could override existing metal-catalyzed reaction conditions

Ⅰ.B.5. Characterization data

Ⅰ.B.5.1. 2, 3-diphenyl pyrazine

Mp.117-121^{0}C ^{13}C NMR ($CDCl_3$, 75MHz): δ 128.2, 128.7, 129.6, 138.5, 142.1 and 152.8

^{1}H NMR ($CDCl_3$, 300MHz): δ 6.38-6.44 (m, 5H, five aromatic hydrogen); 6.55-6.58 (m, 5H, five aromatic hydrogen); 7.72 (s, 2H, 2 aromatic hydrogen of the heterocyclic moiety).

Ⅰ.B.5.2. 2, 3-bis (4-methoxy phenyl) pyrazine

Mp.111-113^{0}C, ^{13}C NMR ($CDCl_3$, 75MHz): δ 55.2, 113.7, 130. 9, 131.2, 141.4, 152.1 and 159.9.

^{1}H NMR ($CDCl_3$, 300MHz): δ 3.77 (s, 6H, 2-OCH3); 6.75-6.85 (m, 4H, four aromatic hydrogen); 7.26-7.43 (m, 4H, four aromatic hydrogen); 8.45 (s, 2H, two aromatic hydrogen of the heterocyclic moiety).

Ⅰ.B.5.3. 2, 3-di p-tolyl pyrazine

^{13}C NMR ($CDCl_3$, 75MHz): δ 21.3, 129.0, 129.4, 135.8,138.5, 141.7 and 152.6.

^{1}H NMR ($CDCl_3$, 300MHz): δ 2.31 (s, 6H, 2-CH3);7.04-7.12 (m, 3H, aromatic hydrogen); 7.22-7.46 (m, 5H, five aromatic hydrogen); 8.51 (s, 2H, two aromatic hydrogen of the heterocyclic moiety).

Ⅰ.B.5.4. 2-methyl-3-phenyl pyrazine

^{13}C NMR ($CDCl_3$, 75MHz): δ 23.1, 128.4, 128.7, 128.9, 138.5, 141.5, 142.1, 151.8 and 154.0

^{1}H NMR ($CDCl_3$, 300MHz): δ 2.54 (s, 3H, -CH_3); 7.46-7.59 (m, 5H, five aromatic hydrogen); 8.44 (d, 2H, J=2.4Hz).

Ⅰ.B.5.5. 2, 3-diphenyl-5-methyl pyrazine

Mp.84-86^{0}C ^{13}C NMR ($CDCl_3$, 75MHz): δ 20.5, 127.4, 127.6, 128.7, 128.8, 137.8, 141.0, 148.8, 150.3, 150.7. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.86 (s, 3H, -CH_3); 6.63 (d, 10H, J-5.1Hz, ten aromatic hydrogen); 7.68 (s, 1H, one aromatic hydrogen of the heterocyclic moiety).

Ⅰ.B.5.6. 2, 3-bis (4-methoxy phenyl)-5-methyl pyrazine

^{13}C NMR ($CDCl_3$, 75MHz): δ 21.2, 53.4, 55.2, 130.8, 130.9,131.2, 131.4, 141.1, 149.0, 150.5, 150. 9, 159.8, 159.6 ^{1}H NMR ($CDCl_3$, 300MHz): δ 2.62 (s, 3H, -CH_3); 3.80 (s, 6H, 2-OCH3); 6.82 (dd, 4H, J=1.8 Hz, four aromatic hydrogen); 7.38 (dd, 4H, J=1.8 Hz, four aromatic hydrogen); 8.39 (s, 1H, one aromatic hydrogen of the heterocyclic moiety).

Ⅰ.B.5.7. 5, 6-diphenyl pyrazine-2, 3-dicarbonitrile

Mp.252-254^{0}C ^{13}C NMR ($CDCl_3$, 75MHz): δ 112.4, 128.2, 129.1, 130.5, 134.5, 154.5, 198.0

^{1}H NMR ($CDCl_3$, 300MHz): δ 7.16-7.30 (m, 5H, five aromatic hydrogen); 7.45 (t, 2H, J=7.3 Hz, two aromatic hydrogen); 7.57 (t, 1H, J=7.3 Hz, aromatic hydrogen); 7.78 (d, 2H, J=7.2 Hz, aromatic hydrogen).

Ⅰ.B.5.8. 5, 6-dip-tolylpyrazine-2, 3-dicarbonitrile

^{13}C NMR ($CDCl_3$, 75MHz): δ 21.6, 126.8, 128.6,129.3, 130.0, 139.2, 144.0, 144.3, 193.3. ^{1}H NMR ($CDCl_3$, 300MHz):δ 2.32 (m, 6H, 2 -CH_3); 6.99 (m, 4H, aromatic protons); 7.43 (m, 1H, aromatic proton); 7.94, (m, 3H, aromatic protons).

Ⅰ.B.5.9. 5-methyl-6-propiopyrazine-2, 3-dicarbonitrile

^{13}C NMR ($CDCl_3$, 75MHz): δ 13.8, 20.4, 22.3, 36.9, 113.3, 113.4, 129.9, 130.4,157.7, 161.2

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.06 (t, 3H, J=7.2Hz); 1.78-1.88 (m, 2H); 2.75 (s, 2H, -CH_3); 2.94 (t, 2H, J=7.5 Hz).

Ⅰ.B.5.10. 2, 3-diethyl 5-methyl pyrazine

Bp. 80^{0}C ^{13}C NMR ($CDCl_3$, 75MHz): 13.1, 13.4, 21.0 , 27.0, 27.69, 116.2, 140.8, 149.9, 152.9, 155.2 ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.25-1.31(m,3H,-CH_3); 2.53, 2.78-2.86(m, 2H); 7.3, 8.2 .

Ⅰ.B.5.11. 2-methyl-3-propylpyrazine

^{13}C NMR ($CDCl_3$, 75MHz): δ 14.0, 21.5, 21.7, 36.9, 141.1, 141.4, 152.3, 156.0.

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.96-1.04 (m, 3H, -CH3); 1.70-1.82 (m, 2H,); 2.57 (s, 3H, -CH3); 2.79 (t, 2H, J=7.5Hz).

Ⅰ.B.5.12. 2, 3 di-(furan-2-yl)-5-methyl pyrazine

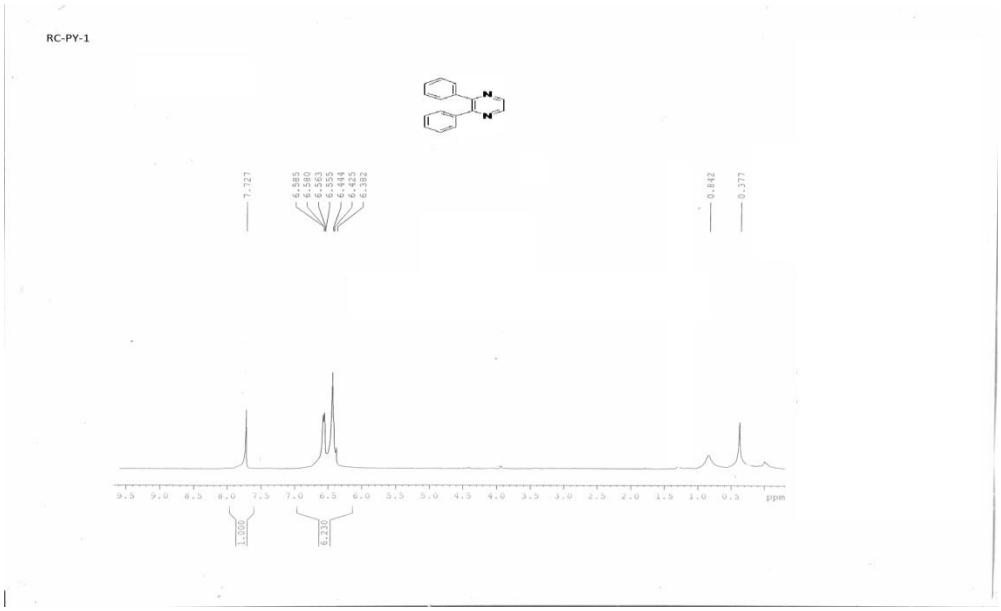
^{13}C NMR ($CDCl_3$, 75MHz): δ 21.3, 112.1, 112.7, 139.2, 140.8, 141.7, 143.4, 143.7, 150.5, 150.6, 151.2. ^{1}H NMR ($CDCl_3$, 300MHz): δ 2.59 (s, 3H, -CH3); 6.56 (m, 4H, aromatic protons); 7.52 (m, 2H, aromatic protons), 8.37 (s, 1H, aromatic proton).

Ⅰ.B.5.13. 1, 4-pyrazine derivative of friedelin

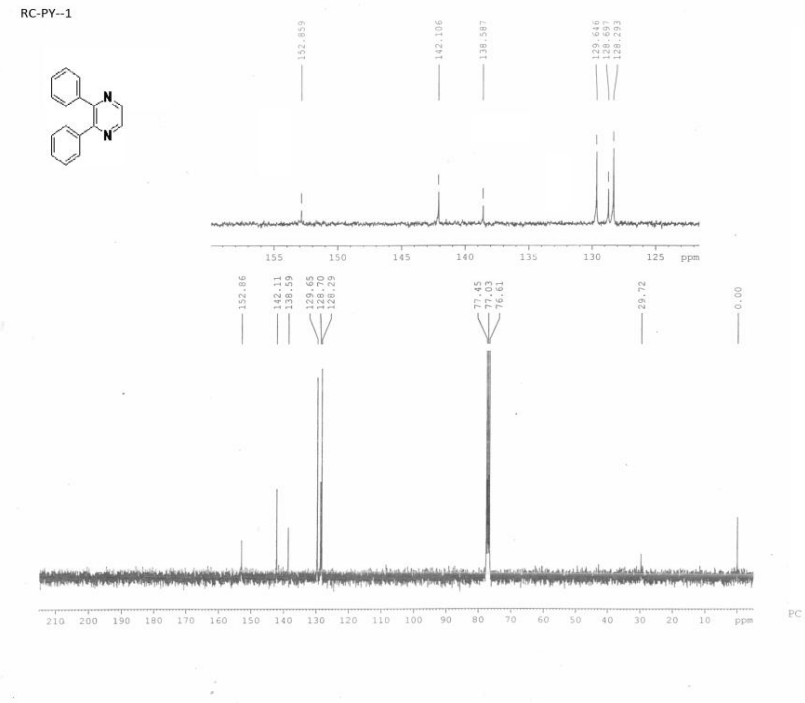
^{13}C NMR($CDCl_3$, 75MHz): δ 150.8, 150.9, 141.4, 142.3

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.82-1.22(7s, 21H, 7t CH_3), 0.99(d, J=6.5 Hz), 8.40 and 8.27 (d, 2H, J=3Hz).

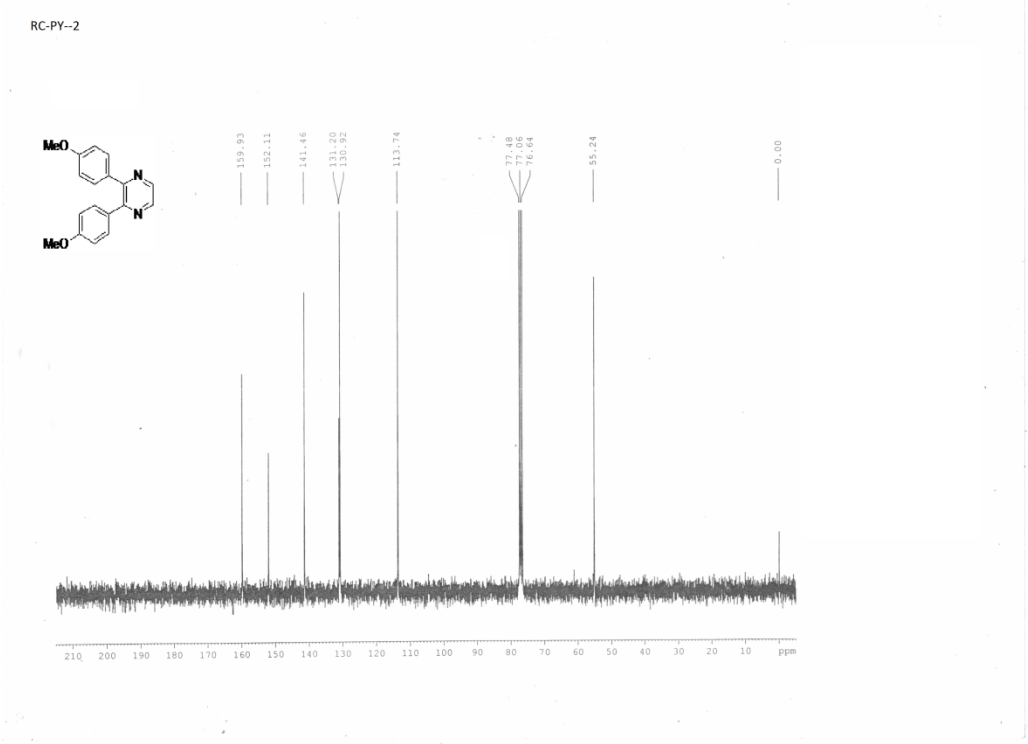
Ⅰ.B.6. Supporting Spectra.



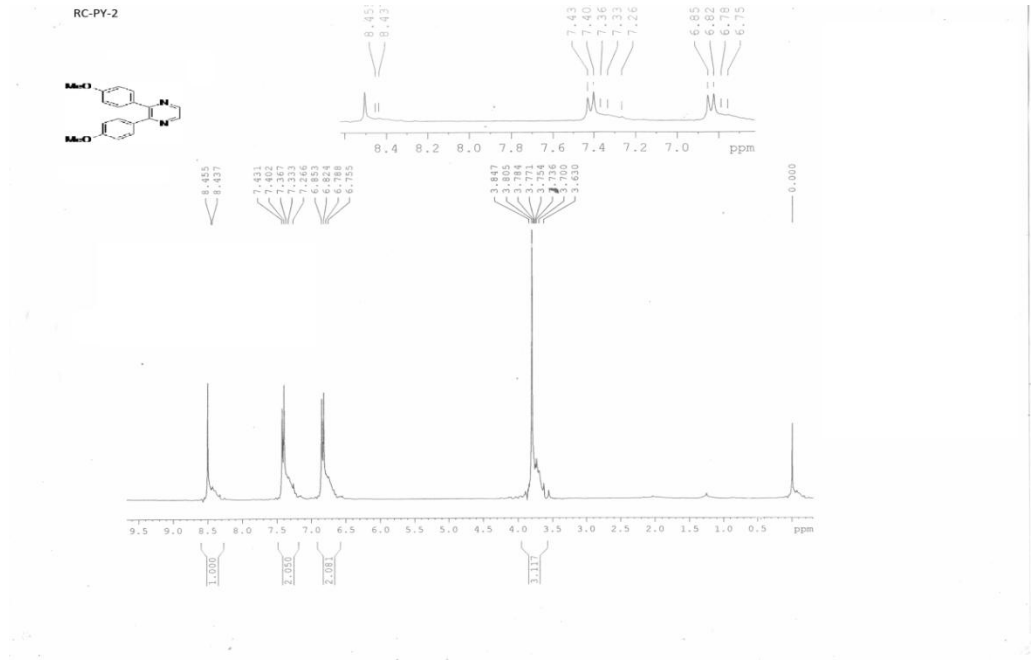
Ⅰ.B.6.1. ^{1}H NMR spectra of 2, 3-diphenyl pyrazine



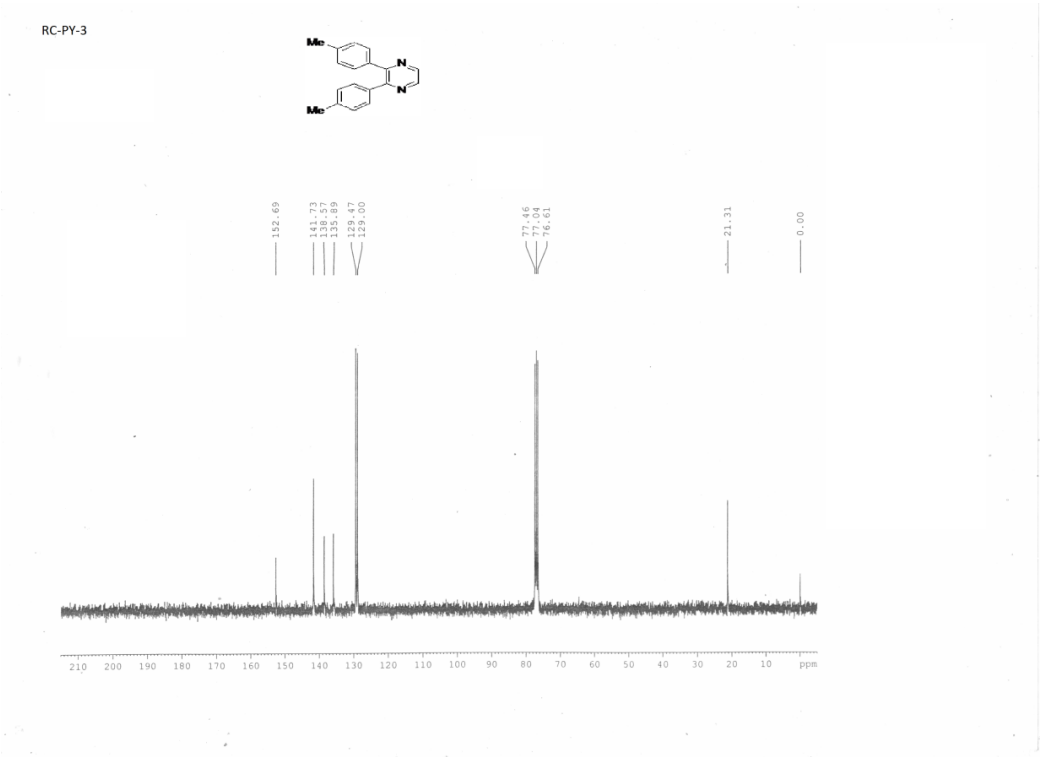
Ⅰ.B.6.2. ^{13}C NMR spectra of 2, 3-diphenyl pyrazine



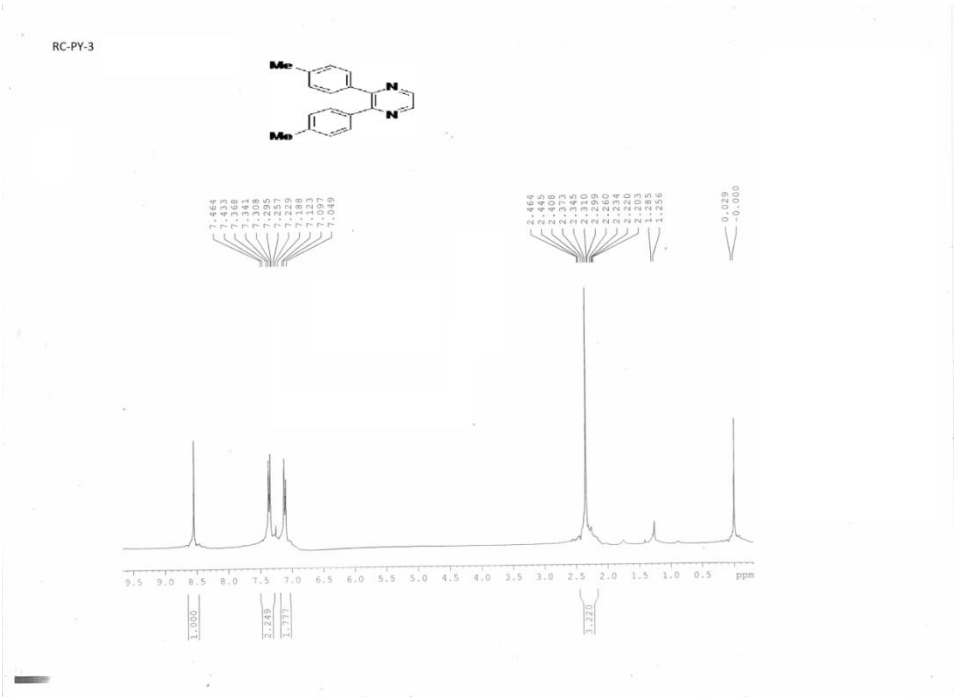
Ⅰ. B.6.3. ^{13}C NMR spetra of 2, 3-bis (4-methoxy phenyl) pyrazine



Ⅰ.B.6.4. ^{1}H NMR spectra of 2, 3-bis (4-methoxy phenyl) pyrazine



I .B.6.5. ^{13}C NMR spectra of 2, 3-di p-tolyl pyrazine



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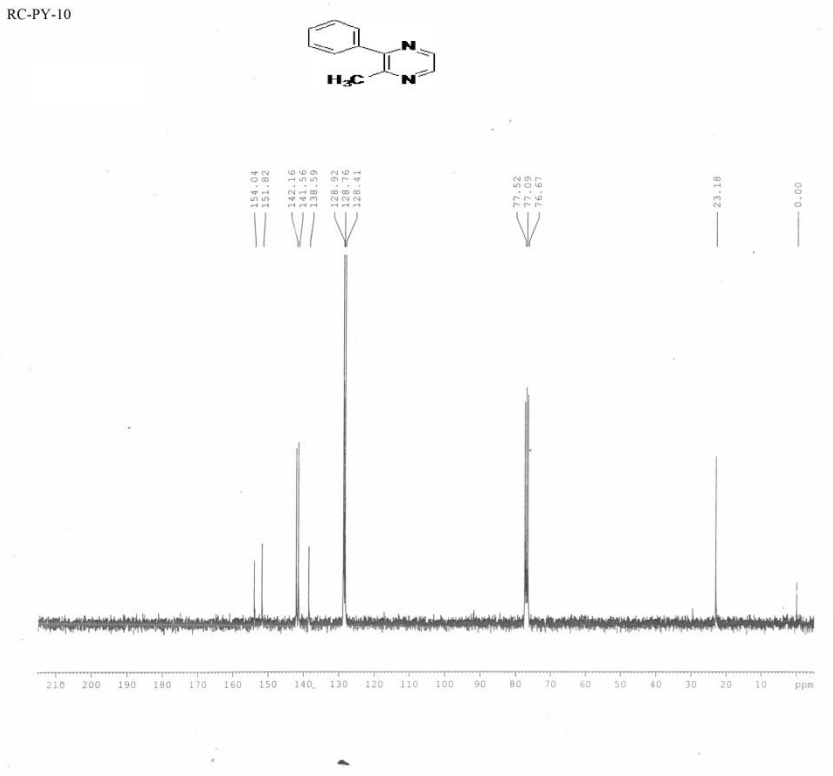
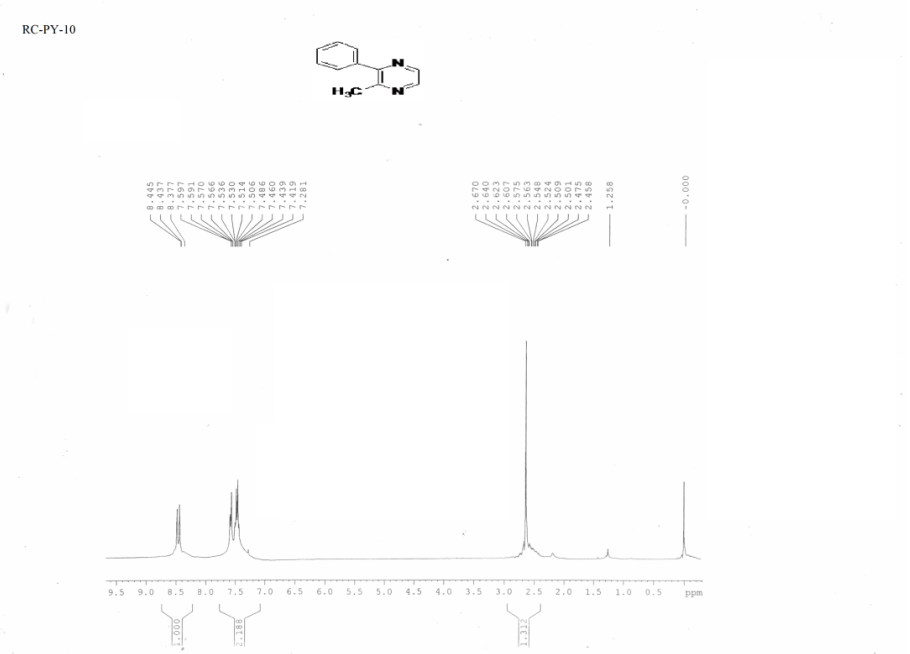
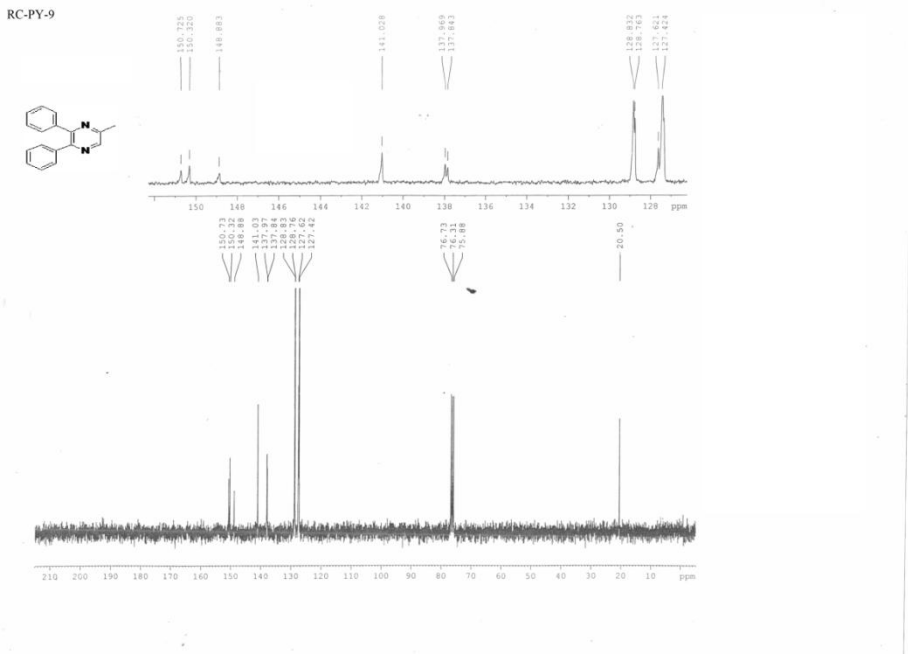


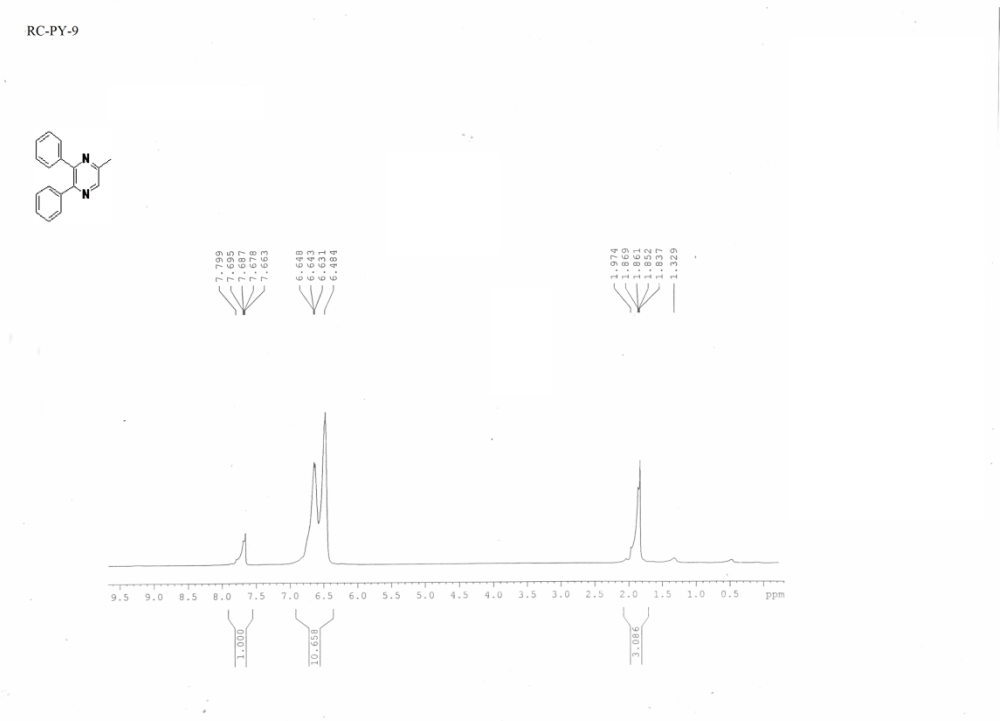
I .B.6.7. ^{13}C NMR spectra of 2-methyl-3-phenyl pyrazine



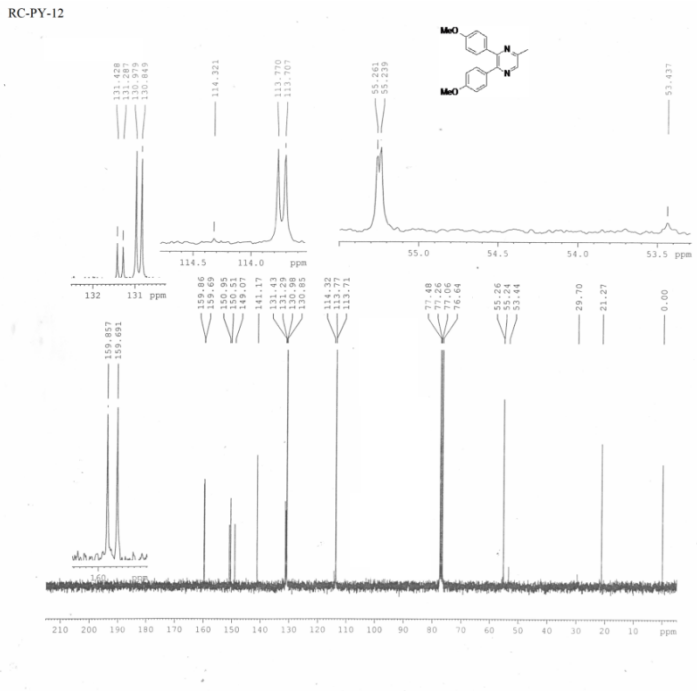
I .B.6.8. ^{1}H NMR spectra of 2-methyl-3-phenyl pyrazine



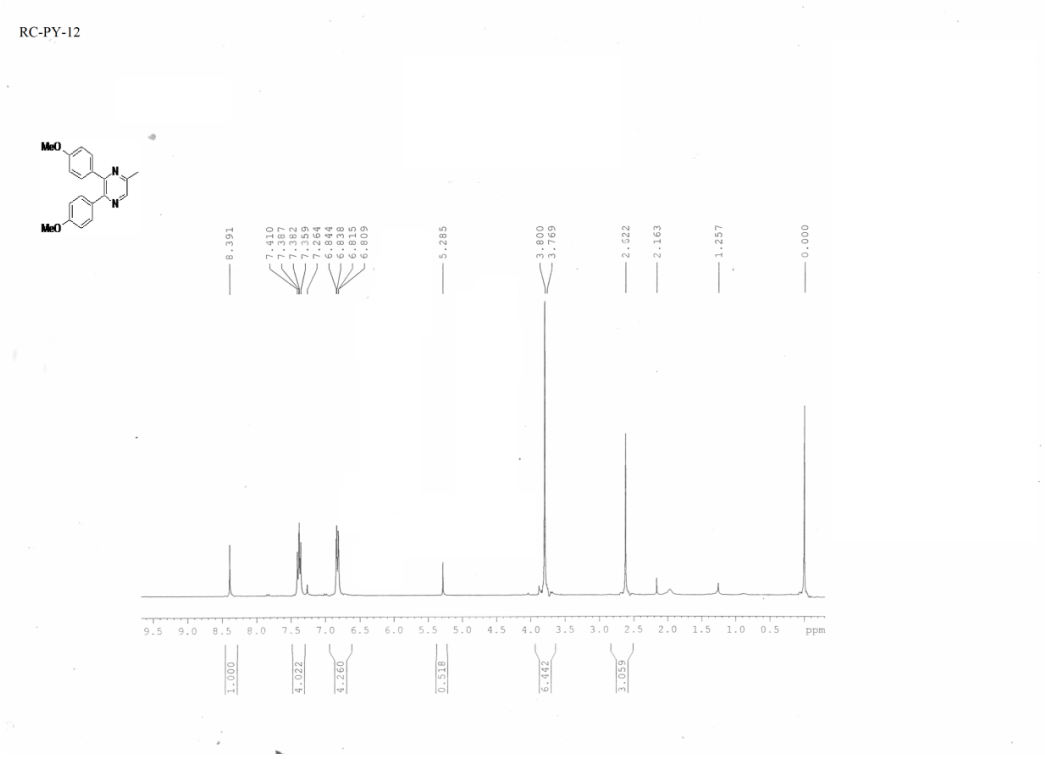
I .B.6.9. ^{13}C NMR spectra of 2, 3-diphenyl-5-methyl pyrazine



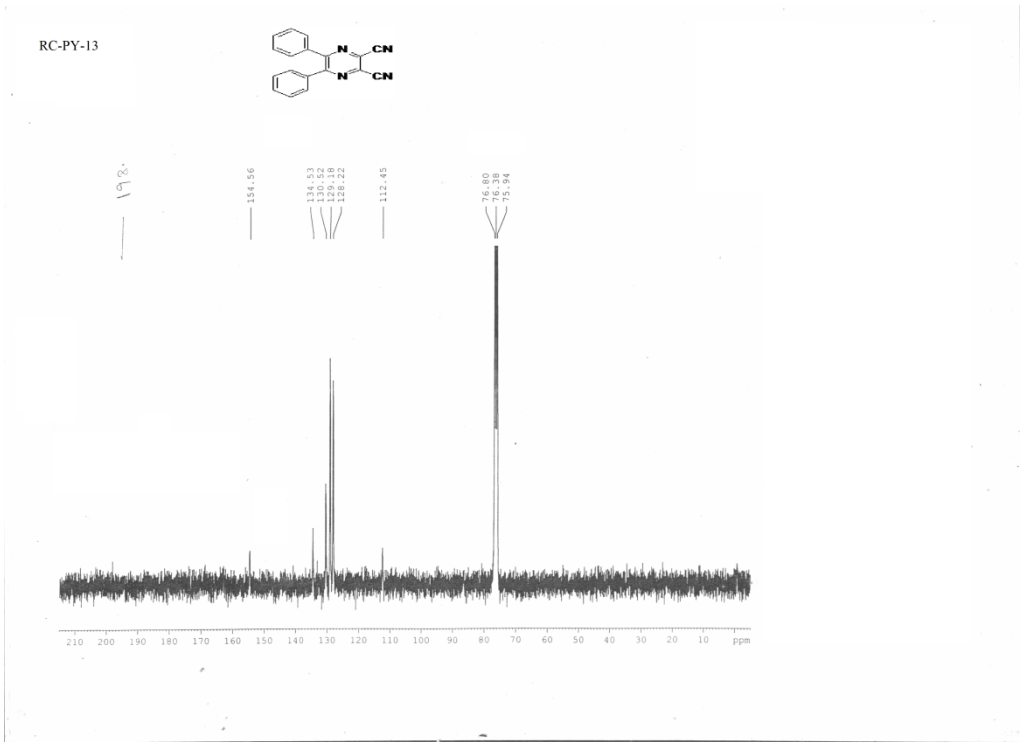
Ⅰ.B.6.10. ^{1}H NMR spectra of 2, 3-diphenyl-5-methyl pyrazine



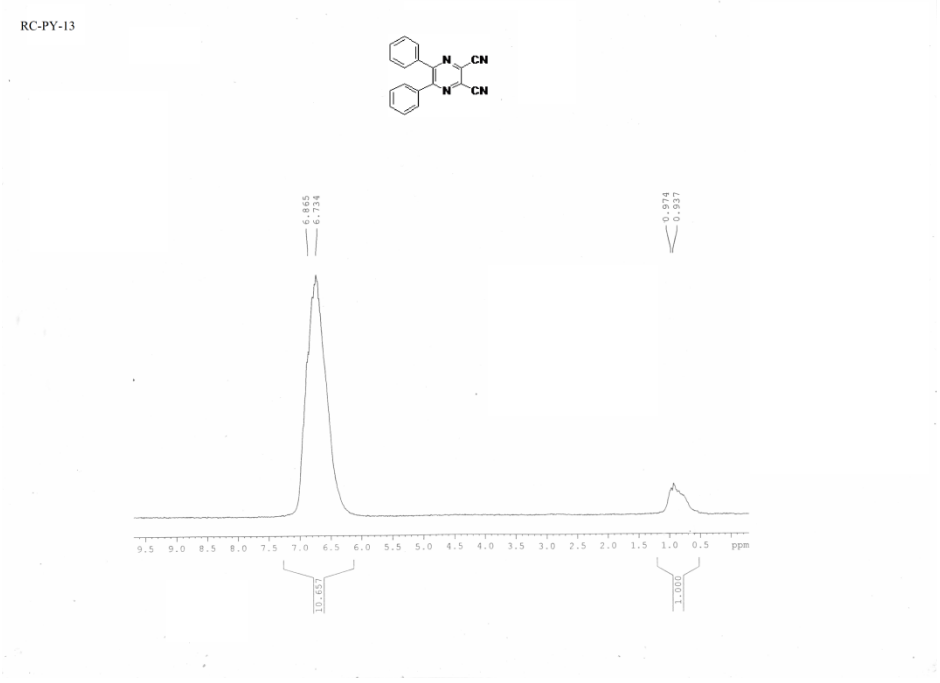
Ⅰ.B.6.11. **^{13}**C NMR spectra of 2, 3-bis (4-methoxy phenyl)-5-methyl pyrazine



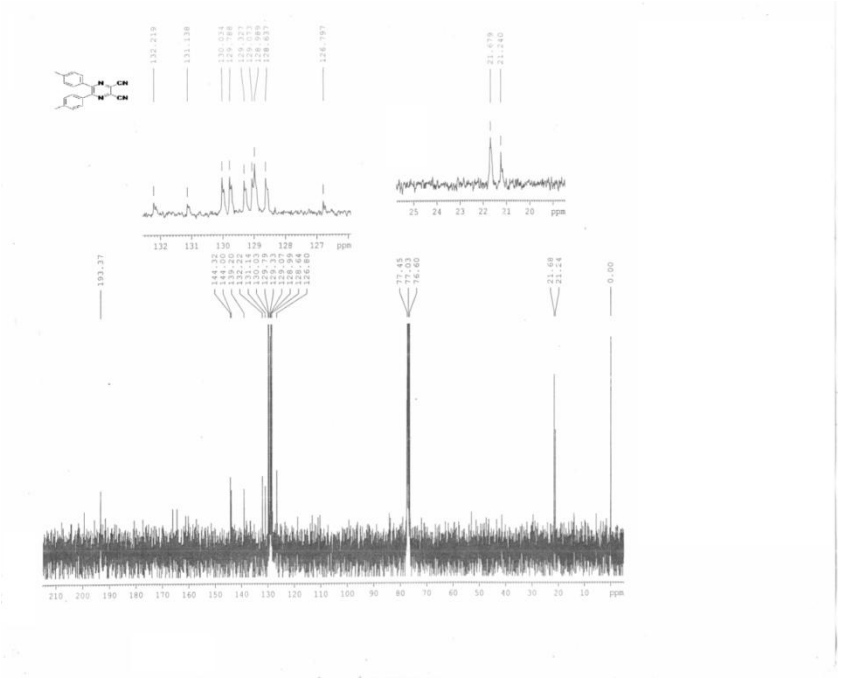
I .B.6.12. ^{1}H NMR spectra of 2, 3-bis (4-methoxy phenyl)-5-methyl pyrazine



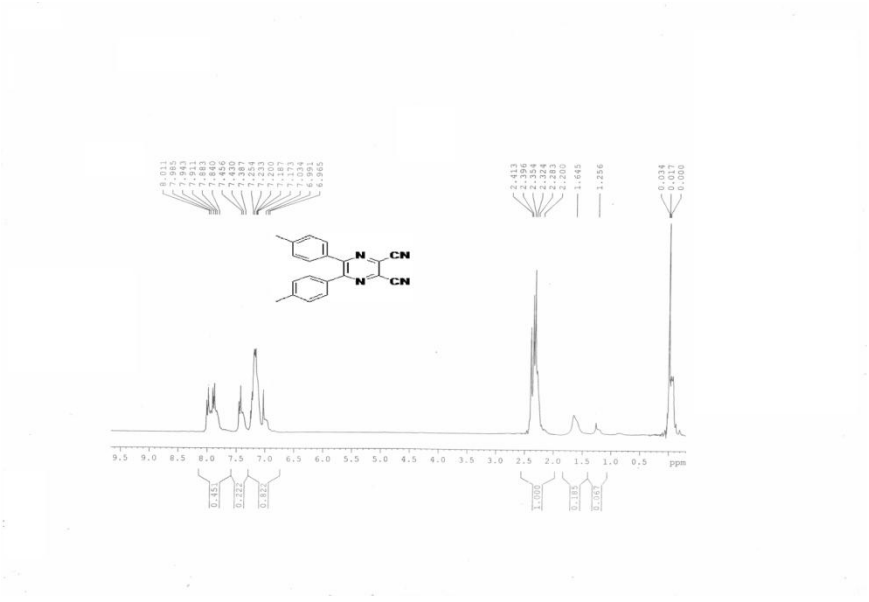
I .B.6.13. [13] C NMR spectra of 5, 6-diphenyl pyrazine-2, 3-dicarbonitrile



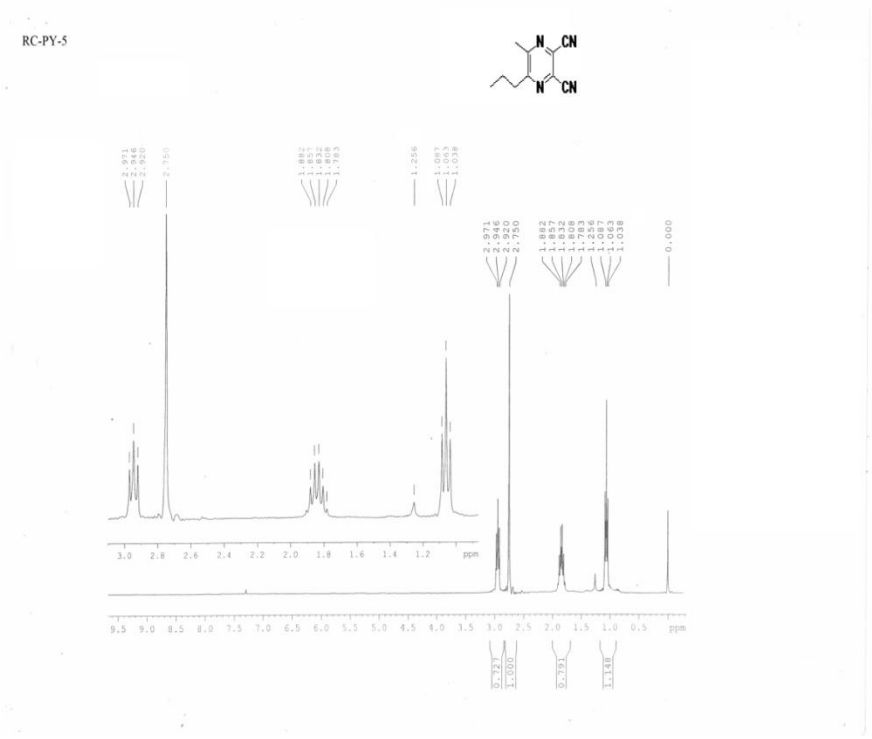
I .B.6.14. ^{1}H NMR spectra of 5, 6-diphenyl pyrazine-2, 3-dicarbonitrile



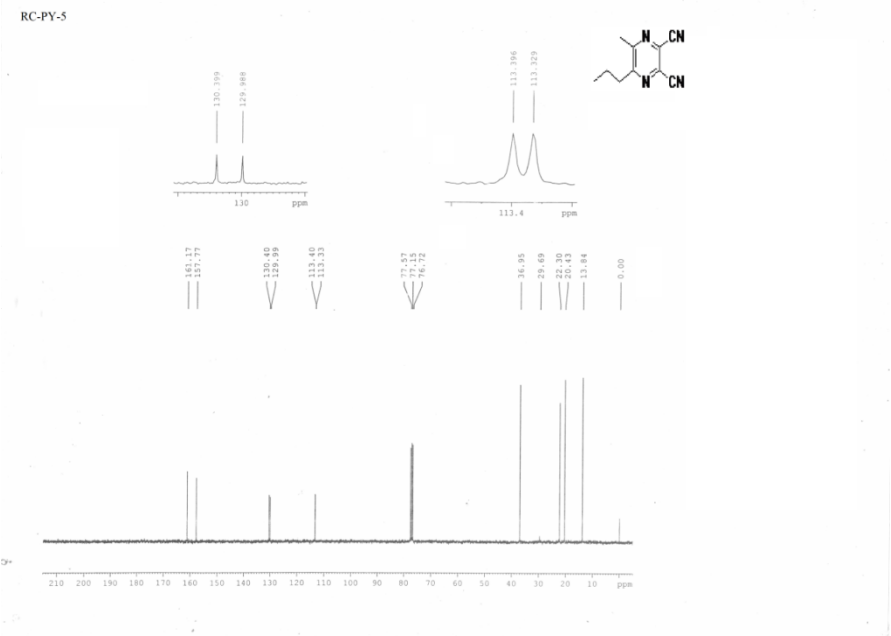
I .B.6.15. ^{13}C NMR spectra of 5, 6-dip-tolylpyrazine-2, 3-dicarbonitrile



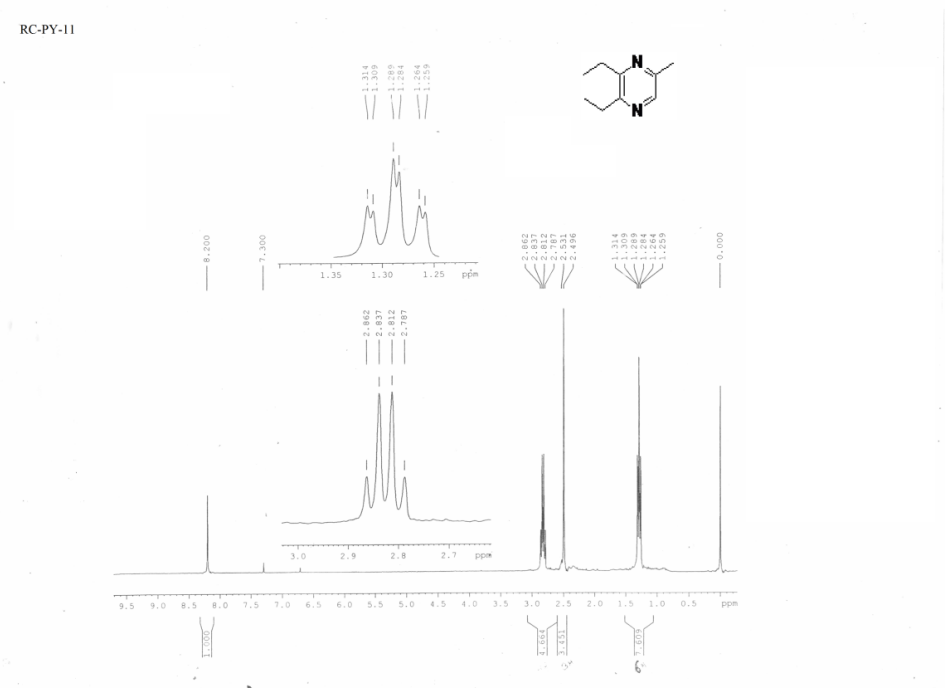
I .B.6.16. ^{1}H NMR spectra of 5, 6-dip-tolylpyrazine-2, 3-dicarbonitrile



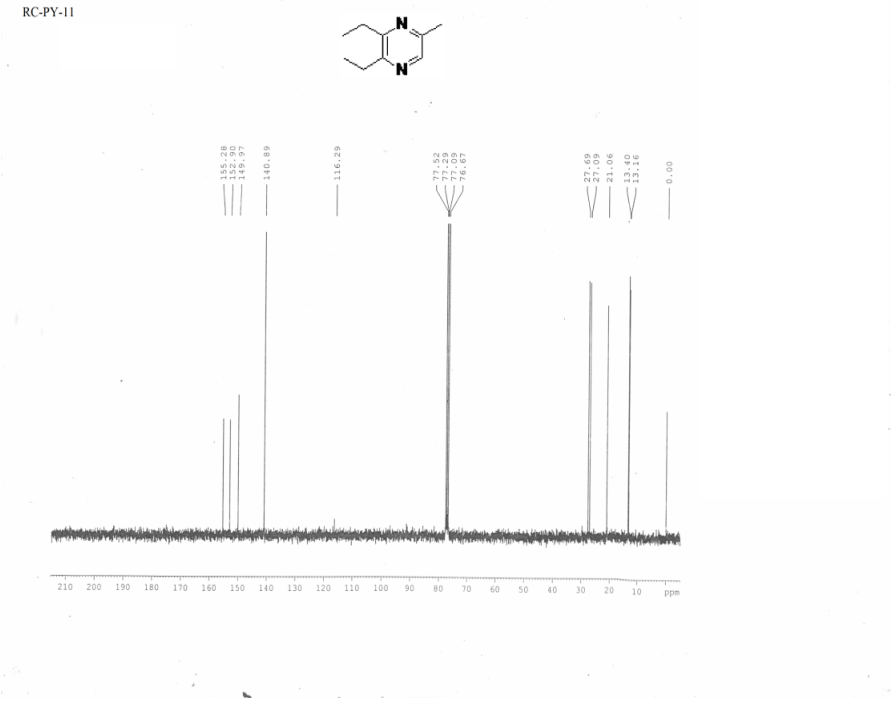
Ⅰ.B.6.17. ^{1}H NMR spectra of 5-methyl-6-propiopyrazine-2, 3-dicarbonitrile



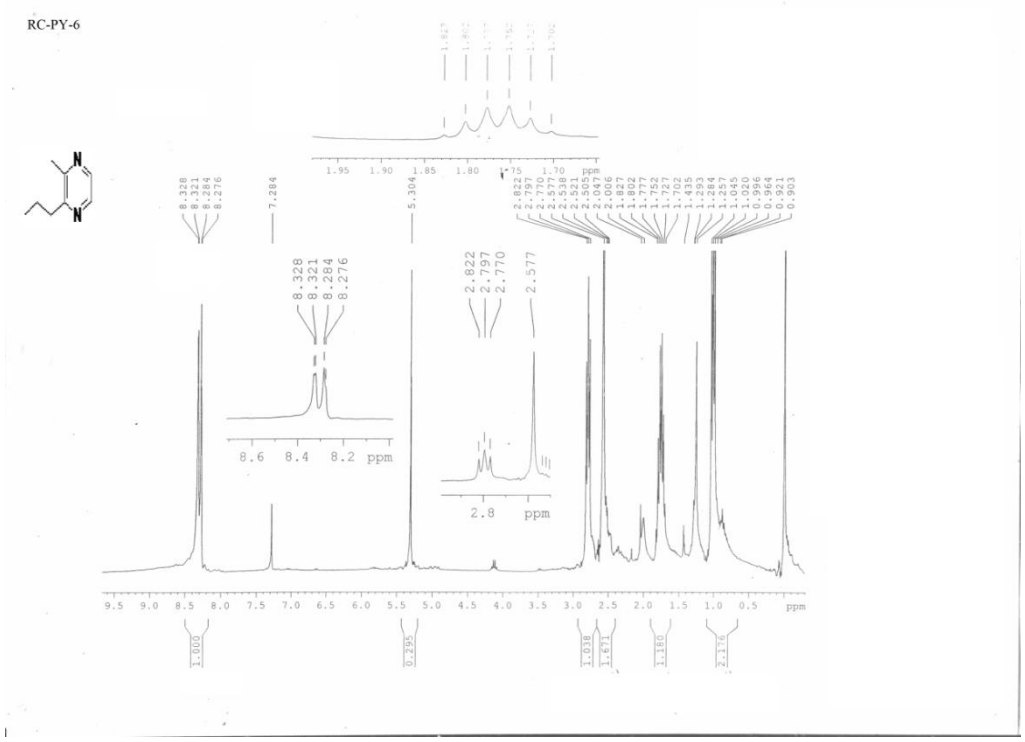
Ⅰ.B.6.18. ^{13}C NMR spectra of 5-methyl-6-propiopyrazine-2, 3-dicarbonitrile



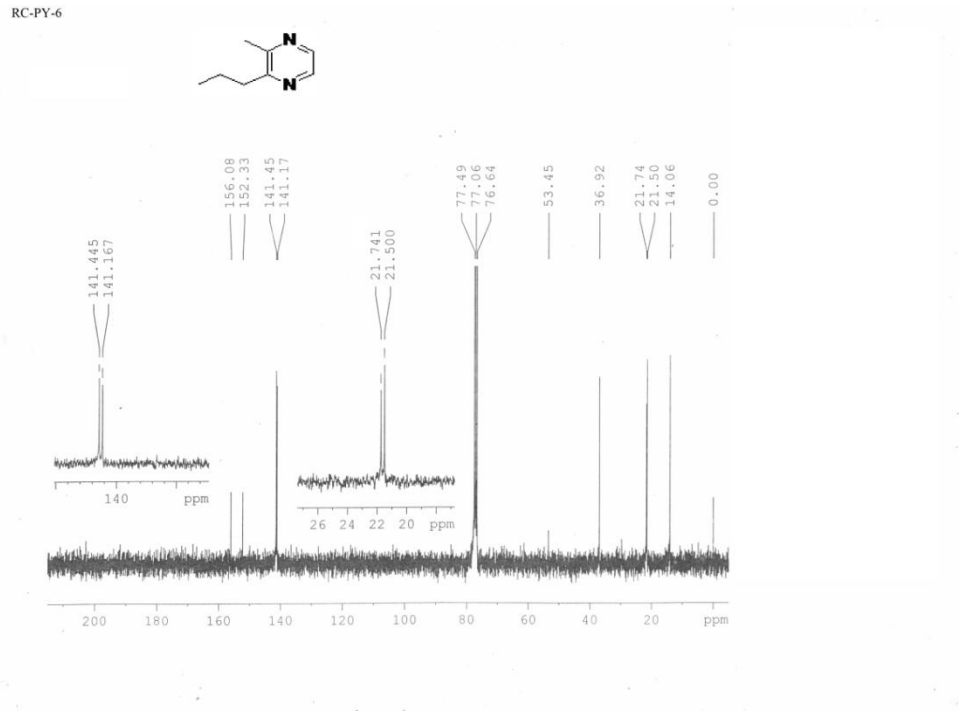
I .B.6.19. ^{1}H NMR spectra of 2, 3-diethyl- 5-methyl pyrazine



I .B.6.20. ^{13}C NMR spectra of 2, 3-diethyl- 5-methyl pyrazine

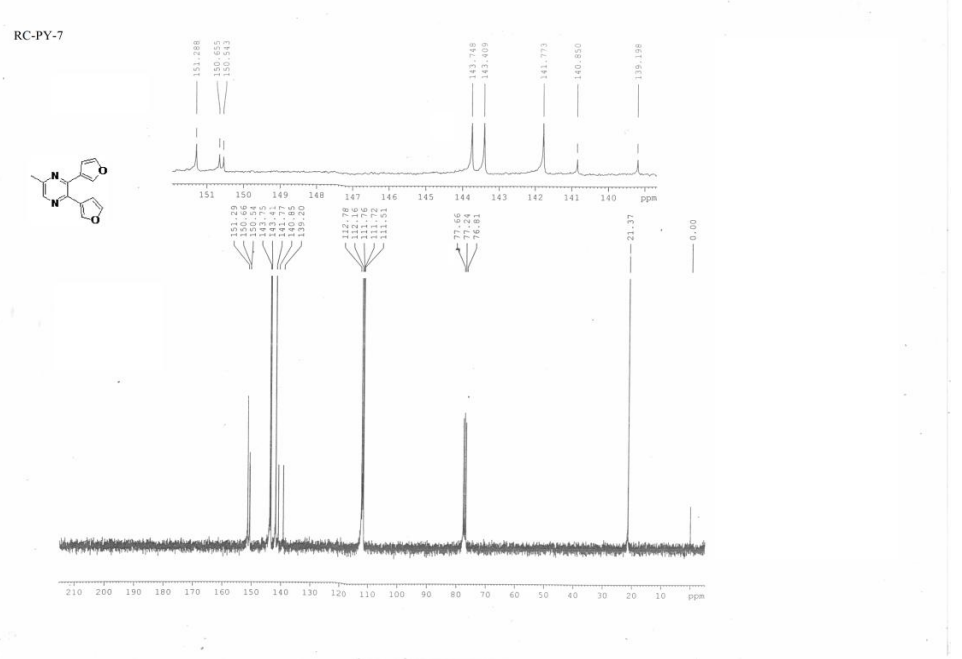


Ⅰ.B.6.21. [1] H NMR spectra of 2-methyl-3-propylpyrazine



Ⅰ.B.6.22. ^{13}C NMR spectra of 2-methyl-3-propylpyrazine

Ⅰ.B.6.23. ^{1}H NMR spectra of 2, 3 di-(furan-2-yl)-5-methyl pyrazine



Ⅰ.B.6.24. ^{13}C NMR spectra of 2, 3 di-(furan-2-yl)-5-methyl pyrazine

Ⅰ.B.7. References

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CHAPTER- Ⅰ

SECTION-C

One-pot synthesis of pyrazines from ethylenediamine and 1, 2-diketones or its analogues catalyzed by Silica-gel

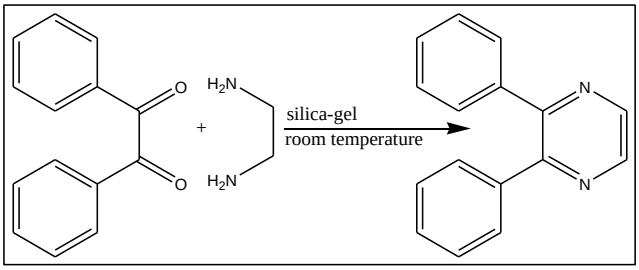
Ⅰ.C. Present Investigation

Ⅰ.C.1. Background of the present Investigation

Heterocyclic compounds are wide spread in nature[1] and compounds containing *N*-heterocyclic moieties are of immense importantance in pharmaceuticals as well as in medicines[2]. Likewise, pyrazine is a class of privileged *N*-heterocycle that is vital components of aroma fragrances,[3] and forms the active core of large number of biologically active substances[4-6]. Pyrazinamide is used against *Mycobacterium tuberculosis* to treat tuberculosis[7]. Cephalostatin, a bis-steroidal marine natural product with a pyrazine core, has been reported to induce apoptosis without the prerequisite of an active caspase-8 and apoptosome formation[8]. Despite their wide agrochemical uses[9], pyrazine derivatives are also used as relaxing cardiovascular, uterine smooth muscle, anti-aggregation, anti-thrombotic, COX-2 inhibiting as well as analgesic effects[10]. These N-heterocyclic compounds, pyrazine and its congeners have broad spectrum of biological activities[11] such as anticancer, antituberculosis[12], antimicobacterial, antimalarial, anti-HIV activity and cytotoxicity[13]. Besides these, pyrazines are widely applied to other industrial fields, for example, in the preparation of pharmaceuticals, perfumes, and agricultural chemicals[14]. It also plays an important role in making flavor ingredient in food and pheromones in various insect[15-16]. It also acts as versatile synthetic intermediates[17]. Due to these wide applications of pyrazine derivatives, their synthesis has always been important for organic chemists. Several synthetic strategies have been developed so far for their synthesis over the years.[18] Pyrazines were formed through catalytic dehydrogenation of the vapour of

ethanolamine. The catalysts used were copper oxide, zinc oxide, copper, sodium carbonate[19]. Condensation of α-amino ketone[20], Pd-catalysed cross coupling reaction also produced pyrazine derivatives[21]. Further, pyrazine compounds were prepared by the reaction of diamine with diol in vapour phase, catalysed by granular alumina[22]. Catalytic system such as copper-zinc-chromium[23], zinc-phosphoric acid-manganese[24], copper-chromium[25] and silver[26] were also used for the preparation of 2-methyl pyrazine from propyleneglycol and ethylenediamine. Pyrazines were synthesized from the condensation of epoxides and diamines using copper-chromium catalyst[27]. Piperazines gets dehydrogenated in the presence of palladium catalyst to produce pyrazines in high yield[28]. α-hydroxy ketones and 1, 2-diamine also produce pyrazines via MnO_2 catalyzed tandem oxidation reaction under refluxing conditions, but the yields were not so encouraging[29], moreover this reaction requires an excess amount of MnO_2 catalyst that detracts from the commercial point of view and green condition[30]. Direct condensation of 1, 2-diketones with 1,2-diamine has so far been the better procedure of pyrazine synthesis through dihydropyrazine[31]. Although there are several methods of pyrazine synthesis in literature, most of them are regarded as ineffective because of poor yield, long reaction time, tedious work-up process and drastic reaction condition[32]. Therefore development of efficient, mild and environmental friendly method for pyrazine synthesis has been a long cherished goal for organic chemists. Since the primary demands of green synthesis include minimization of steps, that is one-pot tandem reactions as well as catalytic processes under metal-free conditions,[33] we explored a greener process for the synthesis of pyrazines directly from simple synthons like ethylenediamine and 1, 2-dicarbonyl compounds or α-hydroxy or α-bromo ketone at room temperature. In recent days, solvent-free synthesis has attracted the attention of chemists because they are environmentally benign processes. In continuation of our interest in the development of solvent-free synthesis,[34] herein we report a new synthetic strategy for the preparation of pyrazine derivatives

catalyzed by silica-gel under solvent-free condition. Silica-gel has been effectively used in organic synthesis not only as a simple medium but also as a mild acid catalyst or as an accelerator. It is easily separable from the product because of its insolubility in organic solvents. Silica-gel supported catalysts such as SiO_2/BF_3, $SiO_2/NaHSO_4$, $SiO_2/FeCl_3$ and SiO_2/H_2SO_4[35] have also been used in various types of organic transformations. With this background of Silica-gel and in connection with our present interest, we envisioned that silica-gel itself could serve as an ecofriendly, easily available and cheap alternative catalyst for the synthesis of pyrazines through the metal-free, solvent-free tandem reduction condensation in one-pot protocol (**Scheme**. Ⅰ.C.1).

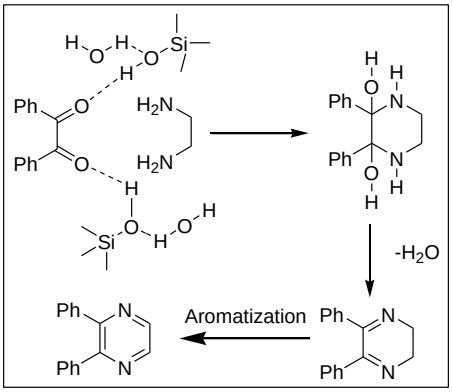


Scheme . Ⅰ.C.1. Silica-gel mediated one-pot synthesis of pyrazines from ethylenediamine and 1, 2-diketones or their analogues.

Ⅰ.C.2.Results and Discussion

In our present investigation we have selected ethylenediamine and benzil for expected transformation.We optimized time(h) for the transformation of ethylenediamine(1mmol) and benzil(1mmol) into pyrazine(Table. Ⅰ.C.1) catalyzed by silica-gel.We mixed benzil(1mmol) and ethylenediamine(2mmol) into silica-gel(2g) at 100^0C under magnetic stirrer for 6h and found no product(**entry 1,table. Ⅰ.C.2.**).Then we took ethylenediamine (1.5mmol), benzil(1.5mmol) and silica-gel(1.5g) at 50^0C and got 42% desired product.Then we conducted the reaction at room

temperature and got 75% product(**entry 3, table. Ⅰ.C.1.**) in identical condition.We added a few drops of water into silica-gel and conducted the reaction at room temperature and got even better result. Finally we optimized the reaction condition as ethylenediamine (1mmol), benzil(1mmol) and silica-gel (1g) with few drops of water and conducted the reaction at room temperature and got 87% yield(**entry 5,table. Ⅰ.C.2.**). In order to show the general applicability, we attempted the developed optimized protocol to a number of chemically diversified ketone and ethylenediamine to synthesize a library of pyrazine derivative (**Table. Ⅰ.C.3.**) and got the desired transformation in each case. The same protocol also gave excellent result (entry 20) when applied on 1, 2-diketo derivative of pentacyclic triterpenoids of lupane or friedelin skeleton (A, B or C). Moreover, it was found that silica-gel was recyclable and only one gram moistened silica-gel is much more effective in the shortest time.The progress of reaction was monitored by TLC. In the present investigation, it is observed that no additional steps required to aromatize the dihydropyrazine derivatives as reported in the early methods and this is the main advantage of this procedure. Optimization of the reaction condition by changing the temperature, time and other condition led us to achieve only pyrazine derivatives as the sole product in (87%) isolated yield. The study also indicates that a trace amount of water on silica-gel is very much effective and a pre-calcined silica-gel is ineffective to bring about the reaction. We depicted a plausible mechanism (**Scheme. Ⅰ.C.2**)



Scheme. Ⅰ.C.2. Plausible mechanisms for the synthesis of pyrazine derivatives using moistened silica gel.

Table. Ⅰ.C.1. Optimization of time(h) for the synthesis of pyrazine from ethylenediamine(1mmol) and benzil(1mmol) catalyzed by silica-gel(1g) at room temperature

Entry	**Time (h)**	**Conversion(%)[a]**
1	12	72
2	5	42
3	7	75
4	8	76
5	**6**	**77[b]**
6	2	34
7	0.5	25

[a]Isolated yield . [b]Optimized condition

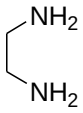
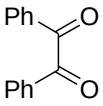
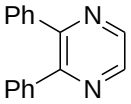
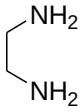
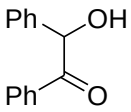
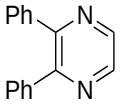
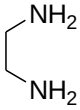
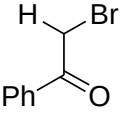
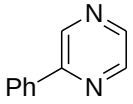
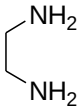
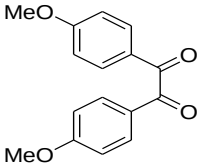
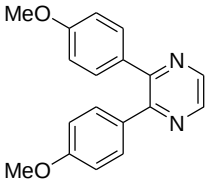
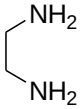
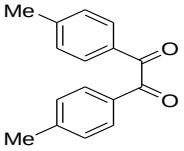
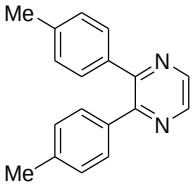
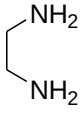
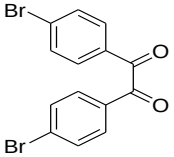
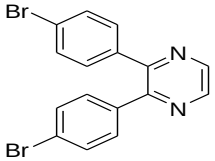
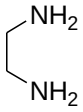
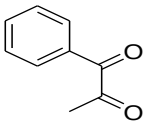
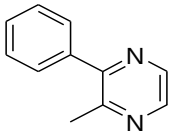
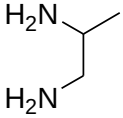
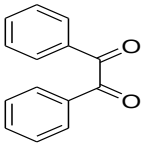
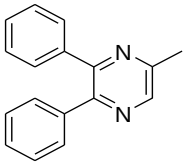
Table. Ⅰ.C.2. Optimization of reaction conditions for silica-gel catalyzed one-pot condensation of ethylenediamine (mmol) with benzil (mmol).[a]

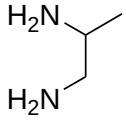
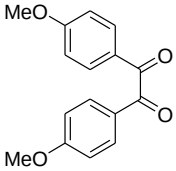
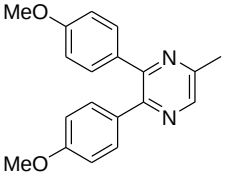
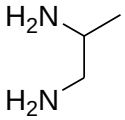
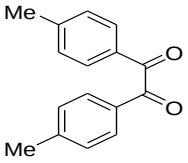
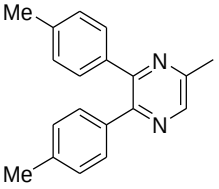
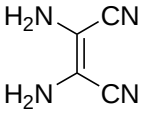
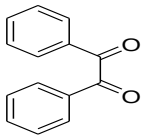
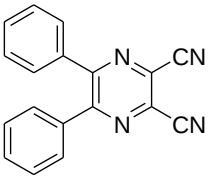
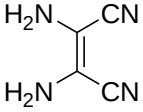
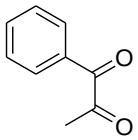
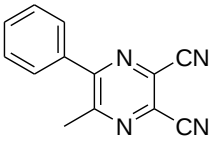
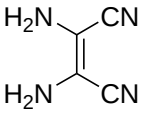
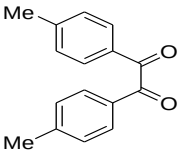
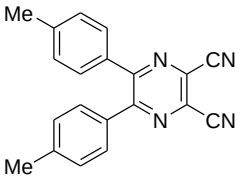
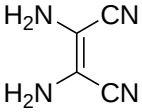
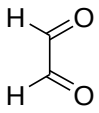
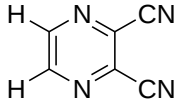
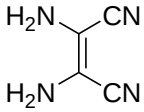
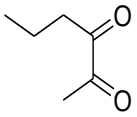
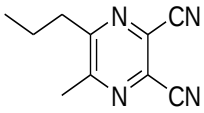
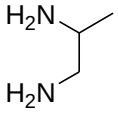
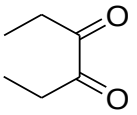
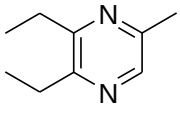
Entry	Silica-gel(g)	Temp(° C)	Solvent	Ethylenedi Amine(mmol)	Benzil(mmol)	Conversion (%)[b]
1	2	100	No	2	1	Nil
2	1.5	50	No	1.5	1.5	42
3	1.0	RT[d]	No	1.0	1.0	75
4	0.5	RT	No	1.0	1.0	62
5	**1.0**	**RT**	**water**	**1.0**	**1.0**	**87[c]**

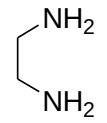
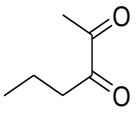
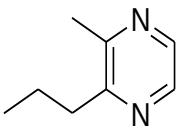
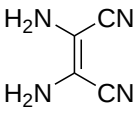
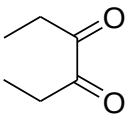
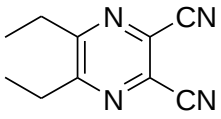
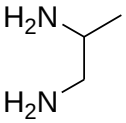
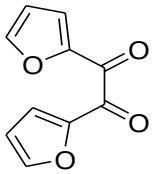
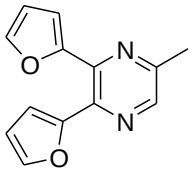
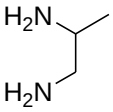
[a]Rection of benzil with ethylenediamine in silica-gel (60-120mesh); [b]Isolated yield; [c]Optimized condition; [d]Room temperature.

In order to show the general applicability, we attempted the developed optimized protocol to a number of chemically diversified ketone and ethylenediamine to synthesize a library of pyrazine derivative (**Table. Ⅰ.C.3**) and got the identical result in each case.The same protocol also gave excellent result (**entry 20, Table. Ⅰ.C.3**) when applied on 1, 2-diketo derivative of pentacyclic triterpenoids of lupine or friedelin skeleton (A, B,or C). Moreover, it was found that silica-gel was recyclable and only one gram moistened silica-gel is much more effective in the shortest time. In the present investigation, it is observed that no additional steps required to aromatize the dihydropyrazine derivatives as reported in the earlier methods and this is the main advantage of this procedure.Melting point of the known compounds are provided in supporting information.[38-39]

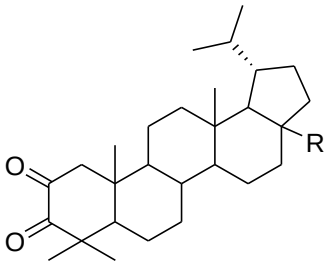
Table. Ⅰ.C.3. Silica-gel catalyzed condensation of ethylenediamine with 1, 2-dicarbonyl compounds or with α-hydroxy ketones or with α-bromo ketone at room temperature

Entry no	Ethylenediamine	1,2-dicarbonyl compound/ analogues	Time(h)	Product	Yield(%)
1			6		87
2			6		75
3			6		68
4			10		76
5			8		81
6			7		80
7			6.5		75
8			5		73

9			5.5		73
10			6		85
11			5		85
12			7		86
13			6		75
14			6.5		82
15			5.5		75
16			7		73

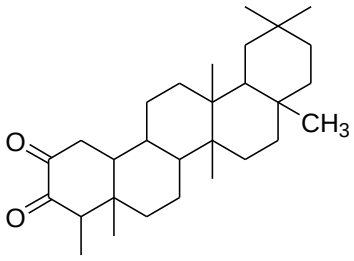
17			8		76
18			7		72
19			5.5		81
20		A/B/C	6	D/E/F	80

Note: % Yield refers to the isolated yield of all compounds. For known compounds, melting points [36-37] and for rest of the compounds respective characterization data are provided in the supporting information

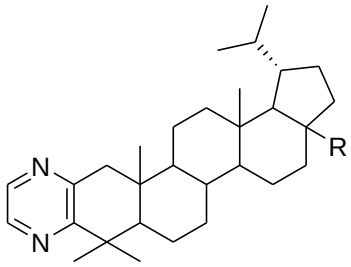


A, R= -CH_3

B, R= -$COOCH_3$

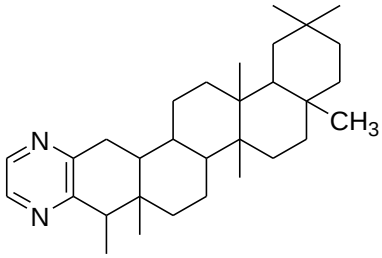


C



D, R= -CH_3

E, R= -$COOCH_3$



F

We also tested the reusability of the catalyst silica-gel (**Table. Ⅰ.C.4**). The catalyst was recovered from the reaction mixture as follows: The reaction mixture was taken in ethylacetate (2 mL), subjected to the centrifugation at 5000 rpm and removed the supernatant liquid. The residue was washed with ethylacetate followed by acetone. Drying under vacuum furnished the powder, which is identical as compared to the first-time used silica-gel.

Table. Ⅰ.C.4. Recycling of the silica-gel tested with ethylenediamine and benzil in one-pot reaction.

Entry	Recovered silica-gel(g)	Silica-gel used	Time(h)	Yield(%)
1st run	___	1g	6	87
2nd run	1g	1g	8	75
3rd run	1g	1g	7	76

Ⅰ.C.3. Experimental

Ⅰ.C.3.1. Reaction procedure and purification

Our studies began with the reaction of ethylenediamine and benzil in the presence of silica-gel. We set-up the reaction by adding the reacting components i.e mixture of ethylenediamine (1mmol) and benzil (1mmol) to the silica-gel(1g) in a mortar, then the mixture was grinded for a few minutes and finally was transferred to a 50 ml round-bottom bottle and was kept under magnetic stirring at room temperature for 6hrs. The completion of reaction was monitored by TLC. Ethylacetate (3×15ml) was added to the reaction mixture and the extract was filtered through anhydrous Na_2SO_4. Finally 2, 3-diphenyl pyrazine was separated by column chromatography over silica-gel(60-120 mesh) where pet-ether and ethylacetate mixture was used as eluent. The desired isolated products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. The reaction condition was optimized in **Table 1**.

Ⅰ.C.3.2. Spectroscopic measurements

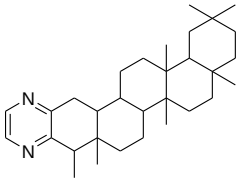
IR spectra was recorded on KBr disks and nujol on Perkin-Elmer FT IR spectrometer. H NMR was recorded on 300 MHz C NMR was recorded on 75 MHz Bruker Avance FT NMR spectrometer using TMS as internal standard.

Ⅰ.C.4. Conclusion

In conclusion, the author has demonstrated the synthesis of bio-active scaffold pyrazine derivatives directly from ethylenediamine and 1, 2-diketone or with its analogues via one-pot condensation reactions using silica-gel as the catalyst under complete metal-free conditions. The conditions are

straightforward, mild and no other side-products are obtained. Green process of preparation of pyrazines from ethylenediamine and keto-compounds are developed that could override existing metal-catalyzed reaction conditions.

Ⅰ.C.5. Characterization data

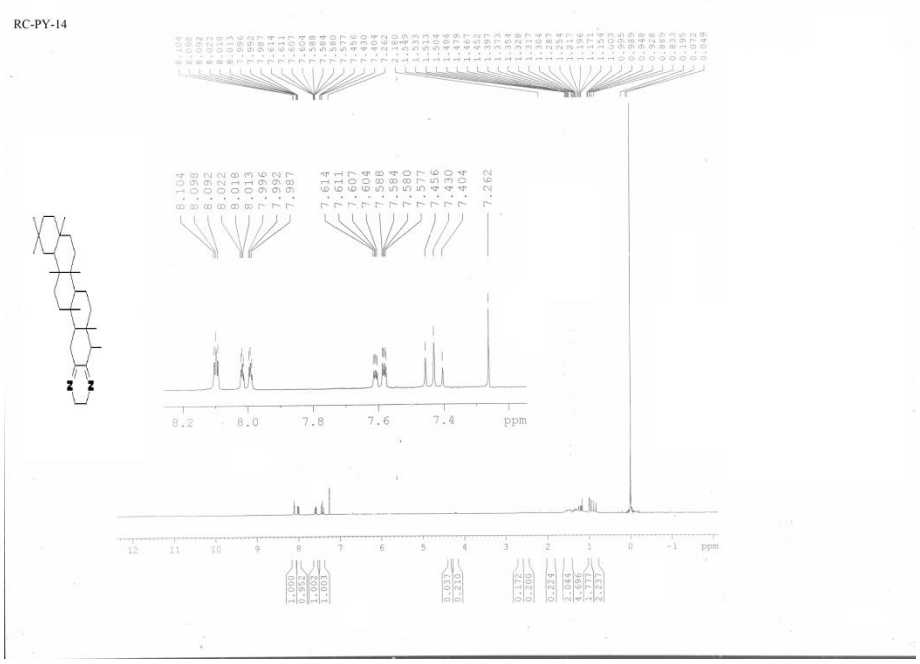


(1) 1, 4-pyrazine derivative of friedelin

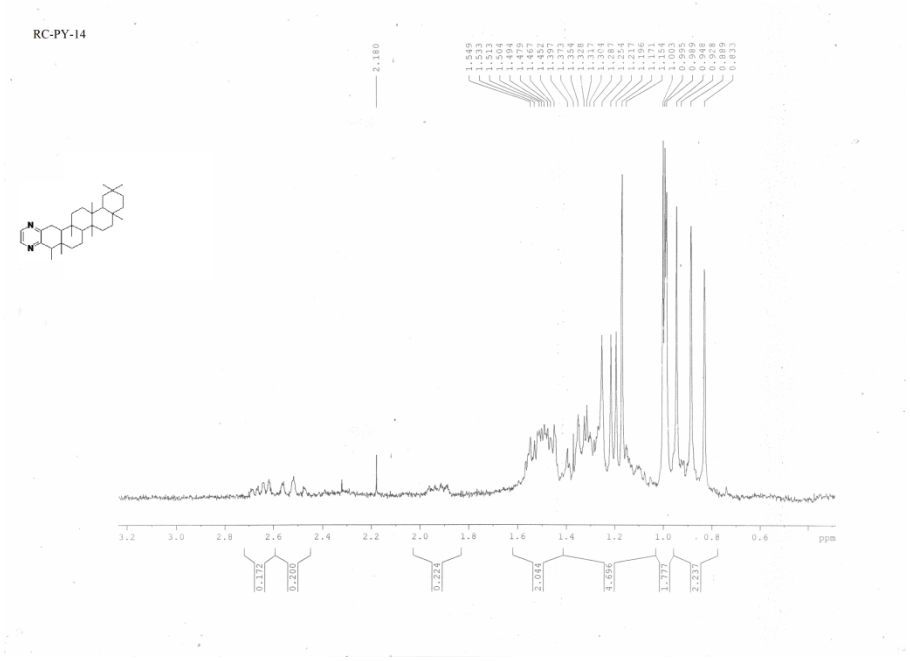
^{13}C NMR($CDCl_3$, 75MHz) : δ 150.8, 150.9, 141.4, 142.3

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.82-1.22(7s, 21H,7t CH_3), 0.99(d, J=6.5 Hz), 8.40 and 8.27 (d, 2H, J=3Hz).

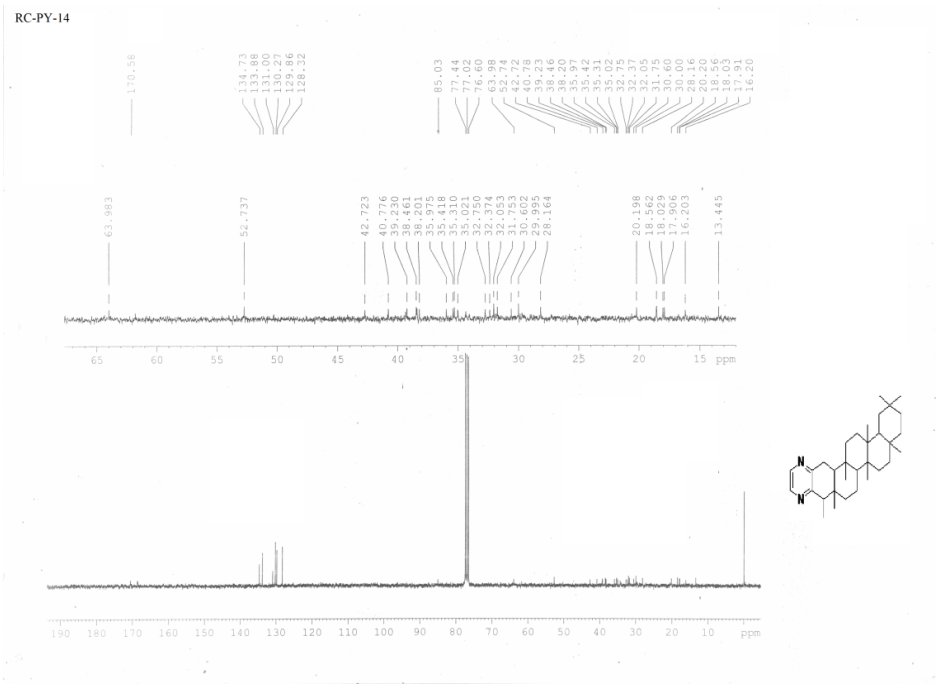
Ⅰ.C.6. Supporting Spectra



Ⅰ.C.6.1. ^{1}H NMR spectrum of pyrazine derivative of friedelin



I .C.6.2. Expanded ^{1}H NMR spectrum of pyrazine derivative of friedelin



I .C.6.3. ^{13}C NMR spectrum of pyrazine derivative of friedelin

Rest characterization data and supporting spetras are attached in Ⅰ-B-6

Ⅰ.C.7. References

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CHAPTER-Ⅱ

Synthesis of Nitriles from Aldehydes and Hydroxylamine hydrochloride on silica-gel

CHAPTER-Ⅱ

SECTION-A

Ⅱ. A. A brief review on nitriles, synthesis and its applications

Ⅱ. A.1. Nitrile

A nitrile is an organic compound which has a –CN functional group. Prefix cyano- is used interchangeably with the term nitrile in industrial literature. Organic compounds containing multiple -CN groups are known as cyanocarbons. Inorganic compounds containing –CN group are not called nitriles, rather cyanides. In spite of the same origin of cyanides and nitriles from cyanide salts, nitriles are generally non toxic. Nitriles include many useful compounds. Milrinone (**fig. Ⅱ.A.1**.), marketed as Primacor, is a nitrile, acts as phosphodiesterase inhibitor used for treating heart failure .[1]

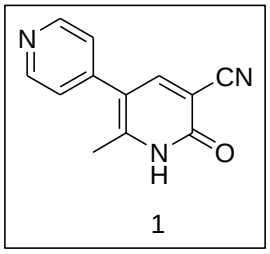

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Fig. Ⅱ.A.1. Milrinone

Methyl cyanoacrylate is a nitrile containing compound, used in super glue and nitrile rubber, a polymer used in laboratory and medical gloves. Nitrile rubber is resistant to fuels and oils, therefore it is used as automotive and other seals. It is also used in the nuclear industry as a protective gloves. Nitrile butadiene rubber is used to make footwear, moulded goods, sponges, sealants and floor mats.

Ⅱ.A.2. Natural occurance of organo nitriles

Nitriles occur naturally in a diverse set of plant and animal sources. Certain seeds and fruit stones, e.g., apricots, apples and peaches, contains cyanides. Cyanides usually bound to sugar molecules to form cyanogenic glycosides[2] in plants.Nitriles are commonly encountered in fruit pits, especially almonds, and cabbage, cauliflower, during cooking, release nitriles through

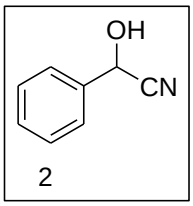

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Fig.Ⅱ.A.2. Mandelonitrile

hydrolysis. Mandelonitrile (**fig.Ⅱ.A.2.) ,** a cyanohydrin produced by ingesting almond or some other fruit pits, releases hydrogen cyanide, which is responsible for toxicity of cyanogenic glycosides.[3]

Ⅱ.A.3. Structure of nitriles

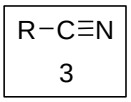

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Fig.Ⅱ.A.3. Structure of nitrile

The geometry of N-C-C is linear in nitriles, which is the characteristic of sp hybridization of the triply bonded carbon. The C-N distance is short (1.16 A^0), consistent with a triple bond. Nitriles are polar, as indicated by high dipole moments.

Ⅱ.A.4. Discovery of organo nitriles

The first compound of nitriles, the nitrile of formic acid, hydrogen cyanide was first prepared by C.W. Scheele in 1782. In 1811, J.L. Gay-Lussac prepared the very toxic and volatile pure acid. In 1832, the nitrile of benzoic acid, benzonitrile, was synthesized by Friedrich Wöhler and Justus Von Liebig, but the yield was poor and due to this reason, physical or chemical properties was not determined. Theophile-Jules Pelouze synthesized propionitrile in 1834, that was believed to be an ether of propionic alcohol and hydrocyanic acid. In 1844, Hermann Fehling prepared benzonitrile by heating ammonium benzoate in a method yielding sufficient quantity for chemical research. Fehling determined the structure of nitrile by comparing the structure of already known synthesis of hydrogen cyanide from heating ammonium formate to his result. He introduced the name "nitrile" for this group of compound.

Ⅱ.A.5. Biological importance of nitriles

Nitriles are a class of compounds having important pharmaceutical and biological role. More than 30 nitrile-containing pharmaceuticals are used for medicinal purpose with more than 20 additional nitrile-containing pharmaceutical leads in clinical development. Vildagliptin (4) , an aminonitrile, is used as an antidiabetic drug, where nitrile bearing carbon is not fully substituted.[4] Pericyazine (5) is an antipsychotic drug, believed to act on several receptors in brain. It is widely used to minimize withdrawal symptoms after drug addiction.[5] Ripivirine (6) is the most potent anti-HIV agent out of many entravirine analogs.[6] Drug anastrazole (7) under trade name Arimidex, marketed by Astra-Zeneca, is used as a drug of choice for treating oestrogen dependent breast cancer.[7]

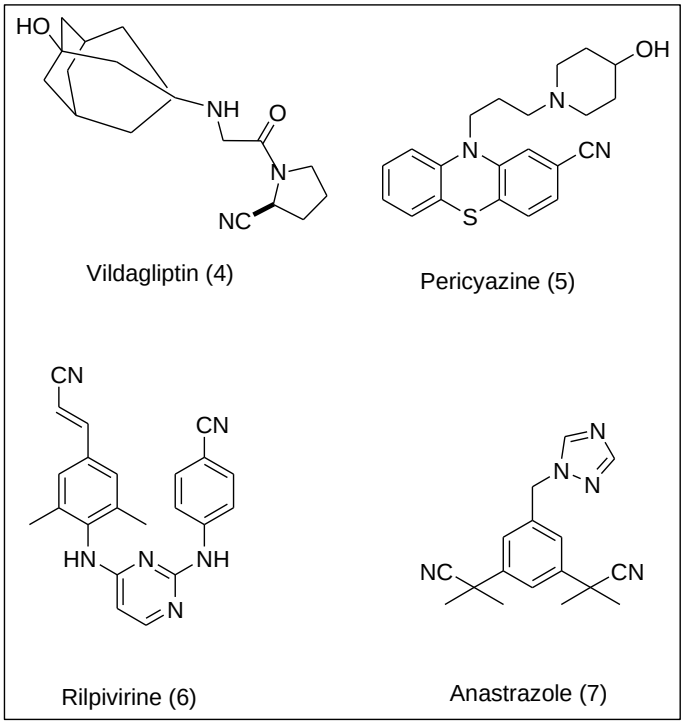
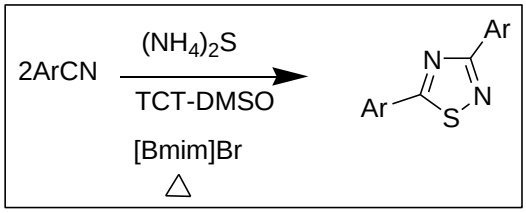


Fig. Ⅱ.A.4. Some biologically important nitrile drugs

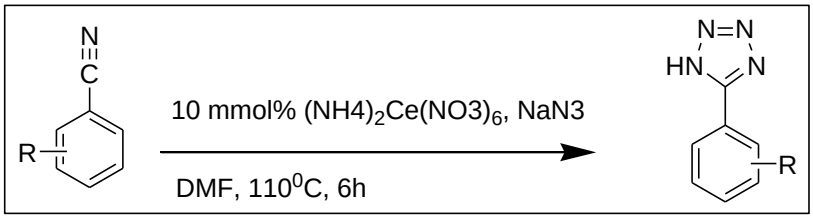
Ⅱ.A.6. Application of nitriles in organic synthesis

Nitriles are important precursor for the synthesis of several nitrogen containing heterocyclic compounds, such as $AgNO_3$ catalyzed synthesis of 5-substituted-1H-tetrazole via [3+2] cycloaddition from the reaction of nitriles with sodium azide.[8] Synthesis of 2-substituted pyrrolidines from nitriles.[9] Synthesis of 3, 5-diaryl-1, 2, 4-thiadiazoles from aryl nitriles in 1-butyl-3-methylimidazolium bromide promoted by $(NH_4)_2S$[10] (**Scheme. Ⅱ.A.1**), Substituted pyridine derivatives are synthesized from two different alkynes and a nitrile using zirconocene and nickel complexes by Tamotsu Takahashi et.al.[11] One-pot synthesis of pyrimidine derivatives.[12]

$(NH_4)_2Ce(NO_3)_6$ catalyzed synthesis of 5-substituted -1H- tetrazoles from nitriles[13] (**Scheme.Ⅱ.A.2**.)

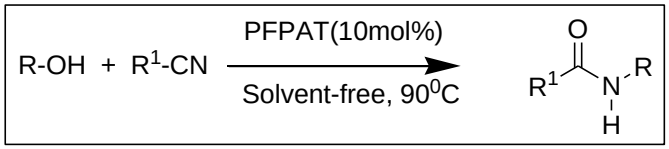


Scheme.Ⅱ.A.1. Synthesis of 3, 5-diaryl-1, 2, 4-thiadiazoles from aryl nitriles



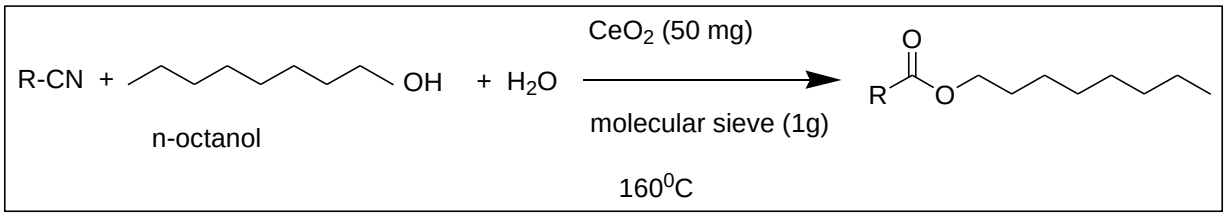
Scheme.Ⅱ.A.2. Reaction of benzonitrile with sodium azide in DMF

Nitriles are also important for functional group transformation from nitriles to another groups and in the synthesis of many important reagents. e.g. synthesis of amides from nitriles via the Ritter reaction[14] (**Scheme.Ⅱ.A.3**),



Scheme.Ⅱ.A.3. Synthesis of amides from nitriles

Masazumi Tamura et.al. synthesized esters from nitriles from the reaction of CeO_2 catalyzed reaction of nitriles with alcohol,[15] (**Scheme.Ⅱ.A.4**)

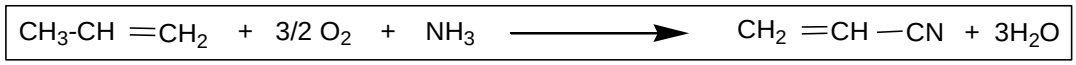


Scheme.Ⅱ.A.4. Synthesis of esters from nitriles

Ⅱ.A.7. Classical method for the synthesis of nitriles

Ⅱ.A.7.1. Ammoxidation

In ammoxidation reaction, a hydrocarbon is partially oxidized in presence of ammonia. Large scale preparation of acrylonitrile is achieved by this process. A side product, acetonitrile is formed during the production of acrylonitrile. Several nitriles are produced by ammoxidation. This process is catalyzed by metal oxides and proceed through imine.[16]

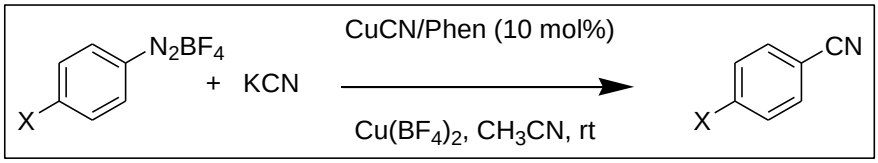


Scheme.Ⅱ.A.5. Synthesis of acrylonitrile from propene

Ⅱ.A.7.2. Sandmeyer reaction

Aromatic nitriles are often prepared from aniline via diazonium compounds. In this reaction, diazonium salt reacts with cuprous cyanide to produce aryl nitrile. Cu(Ⅰ)/Cu(Ⅱ) catalyzed synthesis of aryl nitriles from aryl diazonium salts by KCN was reported by I.P. Beletskaya

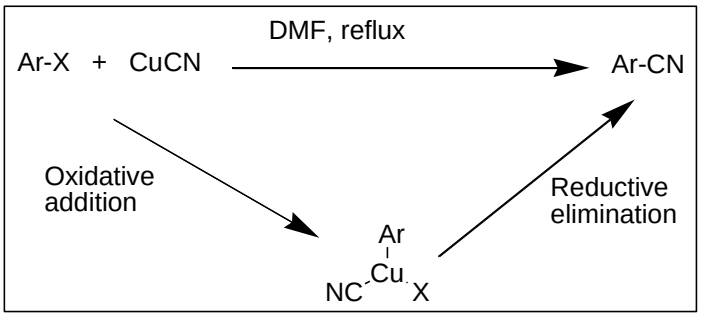
et.al.[17](**Scheme.Ⅱ.A.6**.). Since inorganic cyanides are used in Sandmeyer reaction, the toxicity of reagent makes Sandmeyer reaction less acceptable for nitrile preparation.



Scheme.Ⅱ.A.6. Synthesis of nitrile from aryl diazonium salt and KCN by Cu catalyst

Ⅱ.A.7.3. Rosenmund- Von Braun reaction

Preparation of aryl nitriles by nucleophilic substitution of aryl halides with excess copper (Ⅰ) cyanide in polar and high-boiling solvents such as, nitrobenzene, DMF and pyridine at reflux condition is known as Rosenmund- Von Braun reaction.[18] The mechanism involves the formation of Cu(Ⅲ) entity by oxidative addition of aryl halide followed by reductive elimination give rise to the formation of product (**Scheme.Ⅱ.A.7.)**



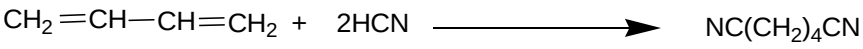
Scheme.Ⅱ.A.7. Synthesis of nitrile from aryl halide and CuCN

Aryl bromides requires drastic conditions(150-280) in this reaction, which is not suitable for sensitive compounds. Besides this, there is few limitation of Rosenmund-Von Braun reaction, e.g. copper(Ⅰ) cyanide used in this reaction is not easily separable from the product nitrile, the polar, high-boiling solvent, high temperature and excess amount of copper cyanide, which makes waste disposal problem, makes Rosenmund-Von Braun reaction less applicable.

Ⅱ.A.7.4. Hydrocyanation

Hydrocyanation[19] is an industrial process for the synthesis of nitriles from the reaction of hydrogen cyanide and alkenes. The process requires homogeneous catalyst. Transition-metal catalyzed addition of hydrogen cyanide across double or triple bonds occur in a Markownicov or anti-Markownicov fashion providing saturated or vinyl nitriles. Generally nickel(0) and palladium(0) complexes are used as a catalyst for hydrocyanation. Nickel-catalyzed hydrocyanation for the production of adiponitrile (1, 4-dicyanobutane) is a precursor of nylon-6,6 from 1, 3-butadiene

(Scheme.Ⅱ.A.8.)

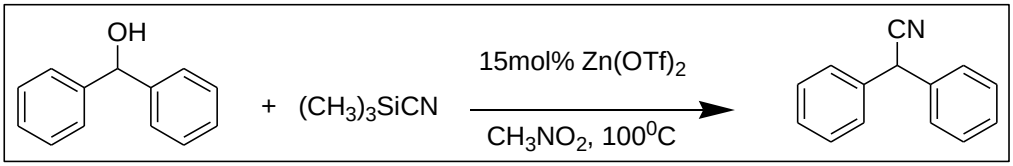


Scheme.Ⅱ.A.8. Synthesis of adiponitrile from 1, 3-butadiene

Ⅱ.A.8. Modern methods for the synthsis of nitriles from different functional groups

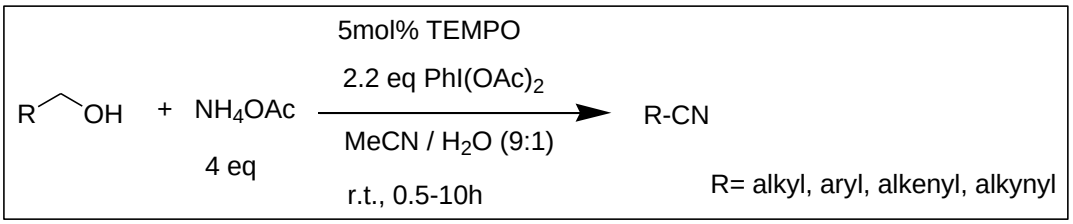
Ⅱ.A.8.1. Synthesis of nitriles from alcohols

P. Theerthagiri and A. Lalitha synthesized α-aryl nitriles from benzylic alcohols directly by $Zn(OTf)_2$ as catalyst[20] (Scheme.Ⅱ.A.9). But this process involves increase in one carbon atom.



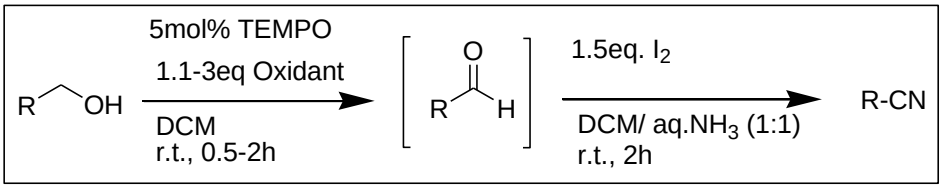
Scheme.Ⅱ.A.9. Synthesis of benzylic alcohol to α-nitrile

J.M.Vatele explored a direct transformation[21] of a wide range of aliphatic, heteroaromatic, benzylic, allylic and propargyl alcohols to nitriles with 2,2,6,6-tetramethyl piperidine-1-oxyl (TEMPO), iodosobenzenediacetate and ammonium acetate, used as a nitrogen source. The reaction proceeds through an oxidation-imination-aldimine oxidation sequence in situ.High chemoselectivity of ammoxidation of primary alcohols in presence of secondary alcohols was also achieved (**Scheme.Ⅱ.A.10.).**



Scheme.Ⅱ.A.10. Direct synthesis of nitriles from alcohols by TEMPO

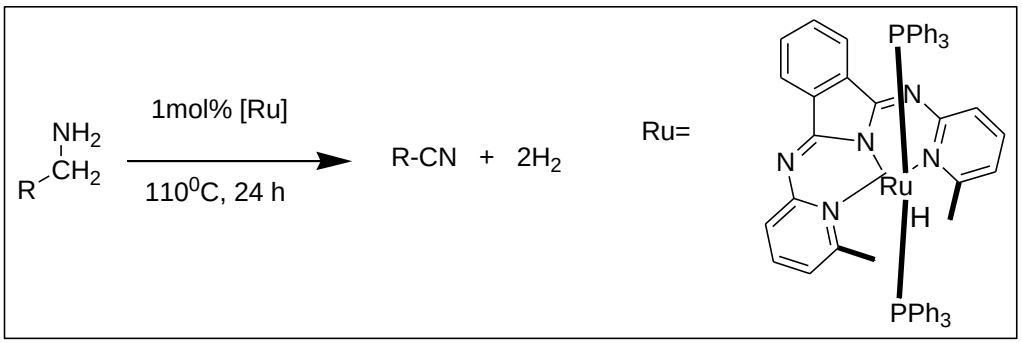
H. Shimojo et.al.[22] synthesized nitriles very efficiently from various alcohol at room temperature. The reaction was catalyzed by tert-butyl hypochlorite, diiodine, or 1, 3-diiodo-5, 5-dimethylhydantoin (DIH) in the presence of TEMPO and then treated with diiodine and aqueous ammonia. The reaction mixture was extracted with chloroform and solvent was removed later. The yield and purity of nitrile was excellent (**Scheme.Ⅱ.A.11.)**



Scheme.Ⅱ.A.11. Synthesis of nitriles from alcohols by DIH

Ⅱ.A.8.2. Synthesis of nitriles from primary amine

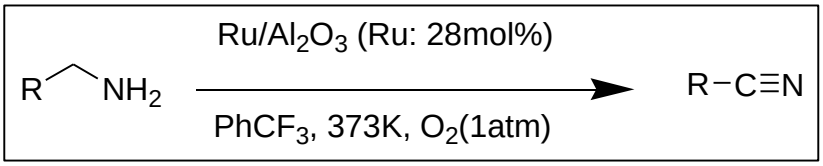
K. N.T.Tseng et. al.[23] explored oxidant-free transformation of primary amines to nitriles. The reaction involves chemoselective dehydrogenation of primary and secondary amines to the corresponding nitriles and imines by an amide-derived NNN-Ru(Ⅱ) hydride complex catalyzed reaction, which is oxidant-free and acceptorless. The reaction is accompanied with liberation of dihydrogen. The reaction is oxidizable functional group tolerant and only primary amines ($-CH_2NH_2$) is susceptible to this reaction in presence of amines without α-CH hydrogens. **(Scheme.Ⅱ.A.12.)**



Scheme.Ⅱ.A.12. Synthesis of oxidant-free nitriles from primary amines

Noritaka Mizuno et.al.[24] synthesized nitriles from primary amines by direct oxidation of amines. They used heterogeneous catalyst Ru/ Al_2O_3 (1.4 wt % of Ru) for the oxidation of amines (activated

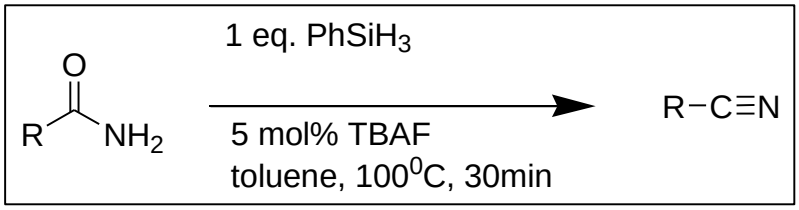
as well as non-activated amines) into the corresponding nitriles with air or 1 atm dioxygen in trifluoro toluene as solvent.(**Scheme.Ⅱ.A.13.)**



Scheme.Ⅱ.A.13. Oxidative transformation of primary amine to nitriles by Ru/Al_2O_3 catalyst

Ⅱ.A.8.3. Synthesis of nitriles from amides

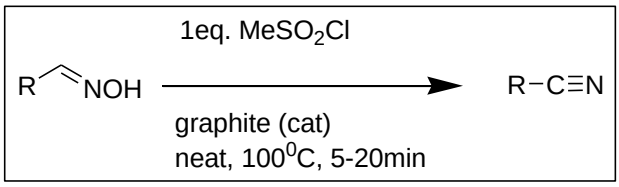
S. Zhou et.al.[25] introduced a convenient protocol for the synthesis of nitriles by catalytic dehydration of aromatic and aliphatic amides using silanes in presence of fluoride (catalytic amount). This protocol allows synthesis of the wide range of aromatic and aliphatic nitriles under mild condition with high selectivity (**Scheme.Ⅱ.A.14.)**



Scheme.Ⅱ.A.14. Synthesis of nitriles from amides using silanes

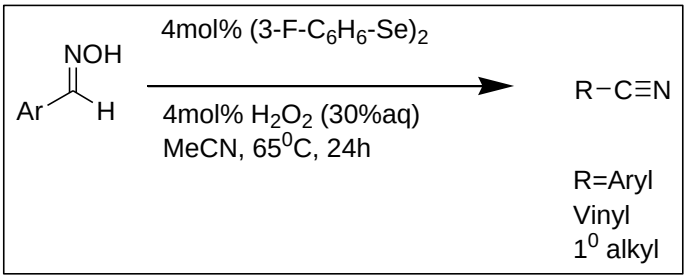
Ⅱ.A.8.4. Synthesis of nitriles from oximes

H.Shargi et.al.[26] synthesized nitriles from oximes by heating with $MeSO_2Cl$, catalyzed by graphite under neat reaction condition at short time (**Scheme.Ⅱ.A.15**.)



Scheme.Ⅱ.A.15. Synthesis of nitriles from oximes under neat condition

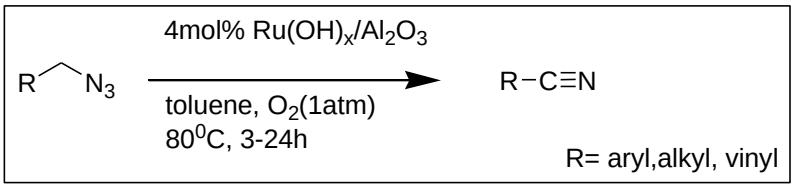
L.Yu.et.al.[27] synthesized nitriles by dehydration of aldoximes by Areneselenenic acids (ArSeOH), which is readily formed from diaryl diselenides and H_2O_2 by oxidation in situ. The catalyst is efficient and recyclable (**Scheme.Ⅱ.A.16.)**



Scheme.Ⅱ.A.16. Synthesis of nitriles from oximes

Ⅱ.A.8.5. Synthesis of nitriles from azides

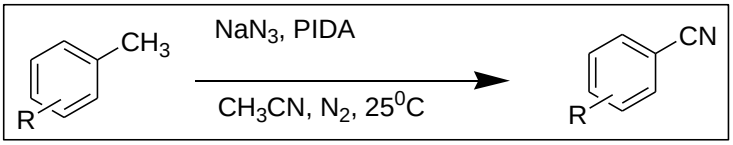
In this methodology, nitriles are prepared from various primary azides, e.g. benzylic, aliphatic, allylic azides by an easily prepared and supported ruthenium hydroxide, $Ru(OH)_x/Al_2O_3$ catalyst into the corresponding nitriles in excellent yields. (**Scheme.Ⅱ.A.17.**)[28]



Scheme.Ⅱ.A.17. Synthesis of nitriles from azides by $Ru(OH)_x/Al_2O_3$ catalyst

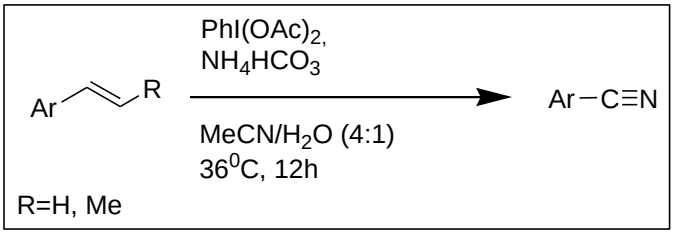
Ⅱ.A.8.6. Synthesis of nitriles from alkenes, alkynes, methyl arenes and benzyl or allyl halides

The direct transformation of alkenes, alkynes, methyl arenes, allyl or benzyl halides are well known in literature. But elongation of one carbon atom takes place in parent compound in these cases. Ning Jiao et.al. [29] reported direct transformation of methyl arenes to aryl nitriles at ambient temperature. In this reaction, they used NaN_3, PIDA, $CuSO_4$, $5H_2O$ in acetonitrile at room temperature (**Scheme.Ⅱ.A.18.)**



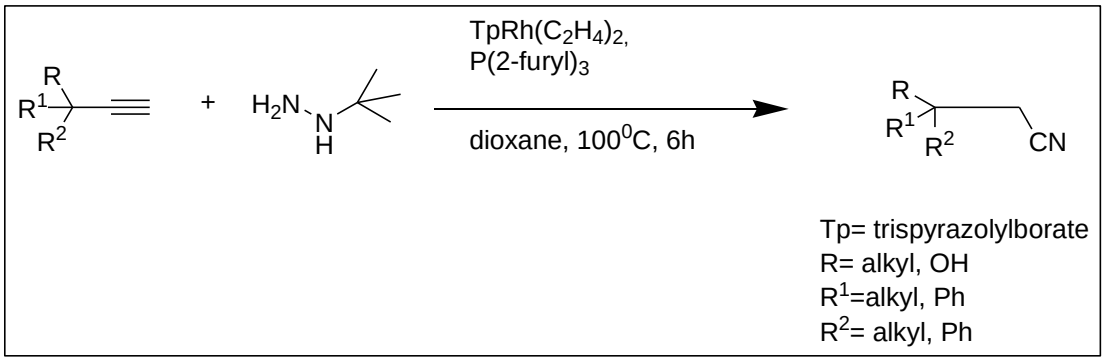
Scheme.Ⅱ.A.18. Synthesis of aryl nitriles from methyl arenes

Synthesis of nitriles from alkenes by metal-free $PhI(OAc)_2$ mediated nitrogenation of alkenes is reported. The reaction proceeds through C=C bond cleavage where inorganic ammonia salt act as a nitrogen source. The reaction is mild which affords nitriles in excellent yield.(**Scheme.Ⅱ.A.19.)**[30]



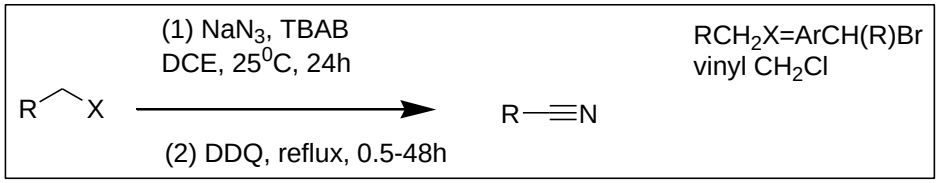
Scheme.Ⅱ.A.19. Synthesis of nitriles from alkenes

Y.Fukumoto et.al.[31] (2016) reported that the combination of $TpRh(C_2H_4)_2$ and $P(2\text{-furyl})_3$ catalyzes the reaction of tertiary alkyl-substituted alkynes with tert-butylhydrazine resulting in the formation of 3, 3, 3-trisubstituted propionitrile derivatives (**Scheme.Ⅱ.A.20.)**



Scheme.Ⅱ.A.20. Synthesis of nitriles from alkynes

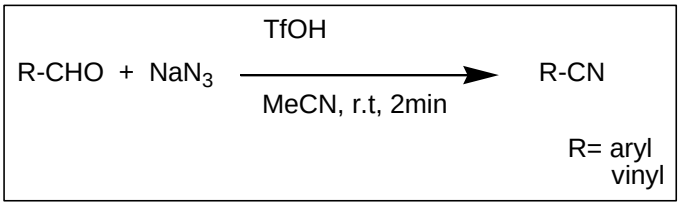
W.Zhou et.al.[32] reported synthesis of aryl or alkenyl nitriles from allyl or benzyl halides by a tandem TBAB- catalyzed substitution followed by novel oxidative rearrangement. The mild reaction condition and broad reaction scope make this method useful in organic synthesis.**(Scheme.Ⅱ.A.21.)**



Scheme.Ⅱ.A.21. Synthesis of nitriles from allyl or benzyl halides

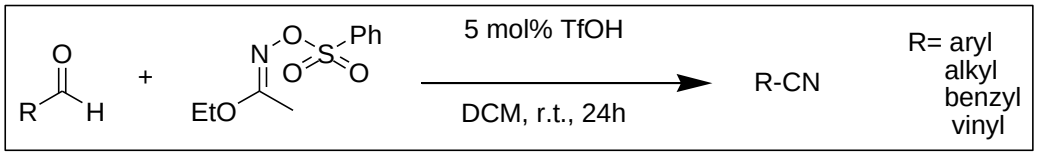
Ⅱ.A.8.7. Synthesis of nitriles from aldehydes

B.V. Rokade et.al.[33] reported Schmidt reaction for the synthesis of nitriles from aldehydes with NaN_3 in near quantitative yield in presence of TfOH and the reaction shows several electron-donating as well as electron-withdrawing functional group tolerance. The reaction is nearly instantaneous (**Scheme.Ⅱ.A.22.)**



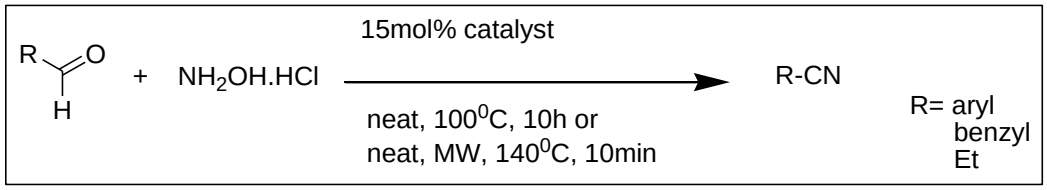
Scheme.Ⅱ.A.22. Synthesis of nitriles from aldehydes by NaN_3

K. Hyodo et.al.[34] (2017) used an O-protected oxime rather than explosive O-protected hydroxylamine for the synthesis of nitriles with a safe Bronsted acid –catalyst via O-protected aldoximes through transoximation (**Scheme.Ⅱ.A.23**.)



Scheme.Ⅱ.A.23. Synthesis of nitriles from aldehydes through transoximation

U.B.Patil et.al.[35] (2013), Synthesized nitriles from aldehydes by an eutectic mixture of choline chloride and urea (1:2) mixture as an efficient and ecofriendly catalyst for this transformation under solvent-free condition. The reaction was carried out under neat and microwave irradiation. The yield was reported to be good to excellent (**Scheme.Ⅱ.A.24.)**

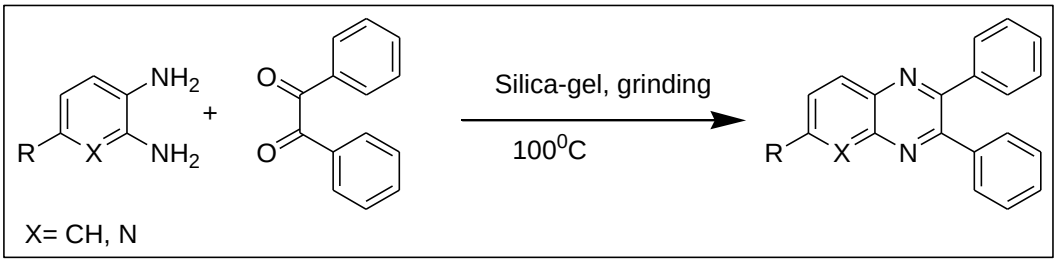


Scheme.Ⅱ.A.24. Synthesis of nitriles from aldehydes by choline chloride and urea mixture (1:2)

Ⅱ.A.9. Application of silica-gel in organic transformations

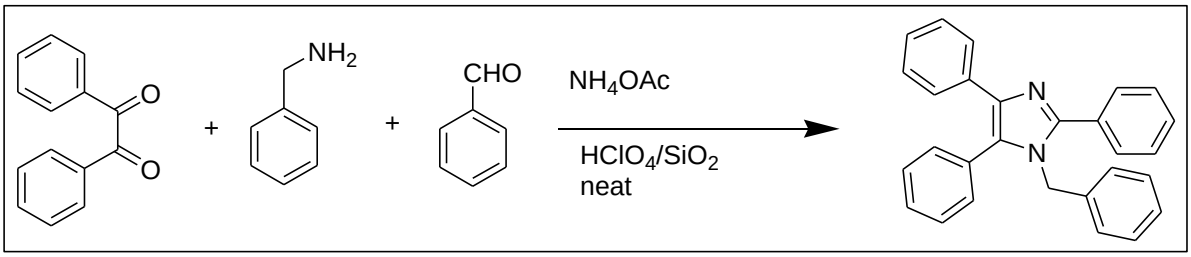
In recent days, solvent-free synthesis have attracted the attention of chemist because the process is environmentally benign. Silica-gel has been effectively used in organic synthesis not only as a simple medium but also as a mild acid catalyst or as an accelerator. It is easily separable from the reaction mixture because of its insolubility in organic solvents. Previously silica-gel has been widely used in many reactions such as – Selective allylation of aldehyde with tetrabutyltin,[36] Selective C-S bond formation, etc. Silica-gel supported catalysts such as $SiO_2/FeCl_3$; $SiO_2/NaHSO_4$; SiO_2/BF_3 and

SiO_2/H_2SO_4[37] have also been used widely in several organic transformation. It is less expensive, ecofriendly and easily available and can easily be separated from reaction mixture. G.C. Nandi et.al.[38] synthesized quinoxaline derivatives from 1, 2-diketones and 1, 2-diamines under solvent-free condition, catalyzed by silica-gel (**Scheme. Ⅱ.A.25**.)



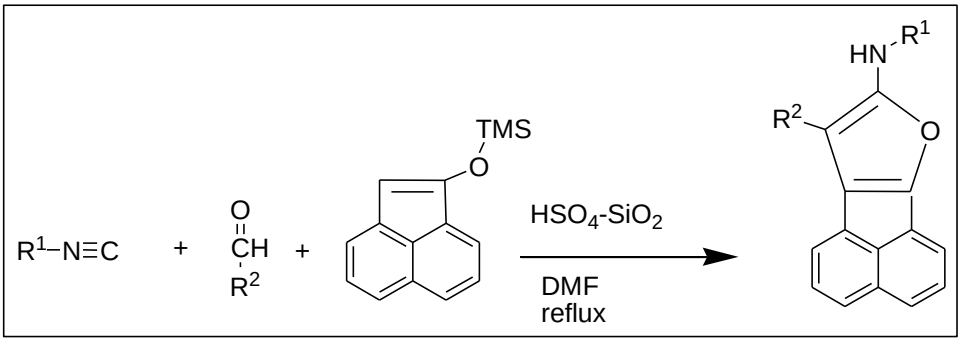
Scheme. Ⅱ.A.25. Synthesis of quinoxalines from benzil with 1, 2-diamine

Kantevary et.al.[39] explored one-pot , highly efficient, four-component synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles from the condensation of diverse aldehydes, benzil, aromatic or aliphatic primary amines and ammonium acetate, catalyzed by perchloric acid adsorbed on silica-gel ($HClO_4$-SiO_2) as catalyst under solvent-free condition. The yield was reported to be excellent and $HClO_4$-SiO_2 exhibited remarkable catalytic activity regarding reaction time (2-20min) and amount of catalyst (**Scheme. Ⅱ.A.26**)



Scheme. Ⅱ.A.26. Synthesis of 1,2,4,5-tetrasubstituted imidazoles catalyzed by $HClO_4$-SiO_2

Cycloaddition reaction of various aldehydes, isocyanides with (acenaphthylen-1-yloxy) trimethylsilane into acenaphtho [1, 2-b]furan derivatives was catalyzed by silica-supported ionic liquid. Sandaroos et.al[40] reported this one-pot transformation (**Scheme. Ⅱ.A.27**.)



Scheme. Ⅱ.A.27. Synthesis of acenaphtho [1,2-b] furan derivatives by silica-supported ionic liquid

Ⅱ.A.10. Conclusion

Nitriles are important bio-active compounds. Besides this, nitriles are useful organic intermediate for the functional group transformations give rise to several nitrogen containing heterocyclic compounds. A lot of catalytic system are reported in literature for the synthesis of nitrile intermediate from different functional group. But most of the methodologies in literature suffer from a few drawbacks e.g. long reaction time, lack of straight-forward process, use and generation of hazardous side-product, tedious work-up process , use of strong oxidizing agents and use of expensive catalyst. Therefore, author explored an easy, low-cost and straight forward protocol by the use of less expensive and environmental friendly reagents for the one-pot synthesis of nitriles.

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CHAPTER-Ⅱ

SECTION-B

Synthesis of Nitriles from Aldehydes and Hydroxylamine hydrochloride on Silica-gel

Ⅱ.B. Present Investigation

Ⅱ.B.1. Background of the present investigation

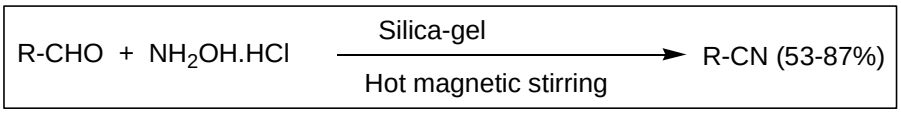
Nitriles are important intermediate for the synthesis of pharmaceuticals, dyes, pesticides, pigments and polymers[1].Nitriles also undergo functional group transformation leading to different types of compounds, e.g. acids[2], amides[3], amines[4], aldehydes[5], esters[6], amidines[7], ketones[8] etc. Nitriles have been widely used for the production of nitrogen heterocycles.e.g. tetrazole[9], pyrrolidines[10], thiadiazoles[11], imidazoles[12], oxazoles[13], and thiazoles[14].Traditional methods of the synthesis of nitriles are sandmeyer reaction[15], Kolbe nitrile synthesis[16], ammoxidation of aldehydes[17], hydrocyanation of alkene[18], etc. There are lot of catalytic system which take part in the transformation of nitriles from different functional group, e.g,from alcohol[19], aldoxime[20,21], amines[22], azides[23], amides[24] and carbonyls[25].Alkene, benzyl or allylhalide and methyl arenes by oxidative rearrangement also yield nitriles. One of the general traditional method for the nitrile synthesis is the nucleophilic substitution of alkyl halide by metal cyanides, however, this method is not attractive due to toxicity of metal cyanides and difficult work-up process. Beside these, all the methods mentioned so far involves increase in one carbon atom of the parent compound.[26-28] Therefore transformation of aldehyde and hydroxylamine hydrochloride into nitrile is an alternative attractive methodology since there is no increase in carbon atom.

Literature survey reveals many catalytic processes for the synthesis of nitriles from aldehyde, e.g, $FeCl_3/NH_2OH$, HCl[29], anhyd $Na_2SO_4/NaHCO_3$ with NH_2OH, HCl under MW irradiation[30],

NH_2OH, HCl/dryAl_2O_3/$MeSO_2Cl$[31],NH_2OH,HCl/anhyd.Na_2SO_4[32],Triethylamine sulfurdioxide[33], montmorillonite KSF[34], formamide[35] , acetohydroxamic acid/$Bi(OTf)_3$catalyst[36]. Although a huge synthetic methodology have been reported, the use of expensive catalyst, long reaction time, different oxidants, toxic metal salts and tedious work-up process makes the existing methodologies avoidable under the aspect of green chemistry. Since nitrile acts as important bioactive material[37] and synthon for designing bioactive molecule, a straight forward , less expensive and environmentally benign methodology needs to be developed. In recent days, solvent-free synthesis has received a lot of attention of chemists because they are environmentally benign processes. In continuation of our present interest in the development of solvent-free synthesis[38], herein we report a new synthetic methodology for the synthesis of nitriles catalyzed by silica-gel under solvent-free condition. Silica-gel has been effectively used in organic synthesis not only as a simple medium but also as a mild acid catalyst or as an accelerator. It is easily separable from the product because of its insolubility in organic solvents. Silica-gel supported catalysts such as SiO_2/BF_3, $SiO_2/NaHSO_4$, $SiO_2/FeCl_3$ and SiO_2/ H_2SO_4[39] have also been used in various types of organic transformations. Considering the background of silica-gel and in connection with our present interest, we envisioned that silica-gel itself could serve as an eco-friendly, easily available, high functional group tolerance and cheap alternative catalyst for the synthesis of nitriles from aldehyde through the metal-free, solvent-free condition in one-pot protocol.

Ⅱ.B.2. Result and discussion

In our present investigation we have selected vanillin as a model compound for the expected transformation.The model reaction consisting of vanillin (1mmol), hydroxylamine hydrochl oride (1mmol) and silica-gel (1g) on magnetic stirrer at room temperature gave no reaction. we went on raising the reaction temperature and found that nitrile (58%) had been formed in 3 h along with trace amount of aldoxime at 70°C .Then we used 1.5 mmol hydroxyl amine hydrochloride and got 63% nitrile at 70°C in 3h. Completion of reaction was tested by TLC. Finally the reaction was optimized as 1.2 mmol hydroxylamine hydrochloride, 1mmol vanillin and 1g silica-gel (60-120 mesh), (**Table.Ⅱ.B. 2. and Table.Ⅱ.B. 3.**) and the reaction mixture was kept on hot magnetic stirrer for four hours at 83^0C and got 87% nitrile (**Table.Ⅱ.B. 1.**). We applied this optimized methodology to different aldehydes and obtained nitriles in 53 to 87% yields (**Table.Ⅱ.B. 3.**). It was found from table1 that aldehydes having electron-donating groups e.g. –OH, -OMe, $-NMe_2$ produced higher yields but aldehydes having electron-withdrawing groups needed higher temperature and produced lower yields. This methodology is applicable to both aromatic and aliphatic aldehydes.



Scheme.Ⅱ.B.1. Synthesis of nitriles from aldehydes and hydroxylamine hydrochloride on silica-gel.

Table. Ⅱ.B.1. Optimization of temperature[a]

Entry	Time(h)	Temp(°C)	Hydroxylamine(mmol)	Yield(%)[b]
1	8	rt	1	Nil
2	3	70	1	58
3	3	70	1.5	63
4	**4**	**83**	**1.2**	**87[c]**
5	5	100	1.2	86
6	6	110	2.0	83

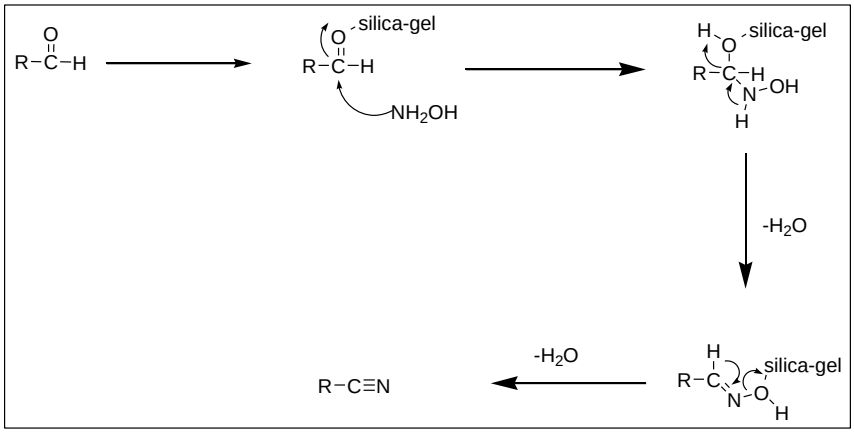
[a]Reaction of vanillin (1mmol), silica-gel 60-120 mesh (1g) on magnetic stirrer in different time and temperature

[b]Isolated yield; [c]Optimized reaction condition.

Table. Ⅱ.B.2. Optimization of catalyst[a]

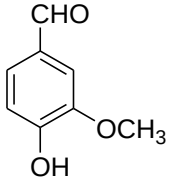
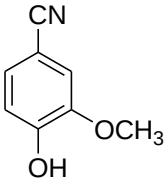
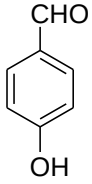
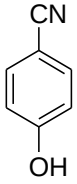
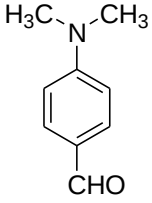
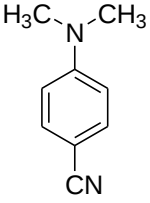
Entry	Silica-gel (g)	Yield(%)[b]
1	nil	Oxime
2	0.5	53
3	**1.0**	**85[c]**
4	1.5	84
5	2.0	75

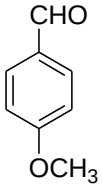
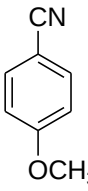
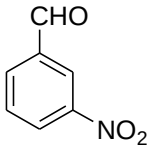
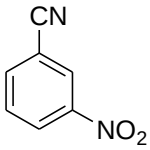
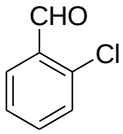
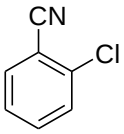
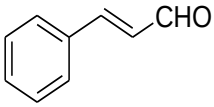
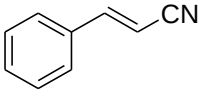
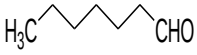
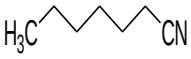
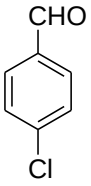
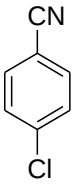
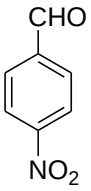
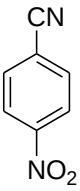
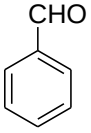
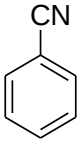
[a]Reaction of vanillin (1mmol), Hydroxylamine hydrochloride (1.2mmol), silica-gel (60-120 mesh in different amount ; [b]isolated yield**.**

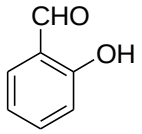
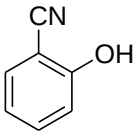
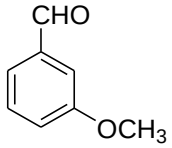
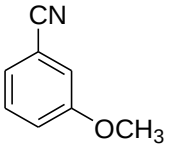
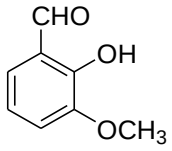
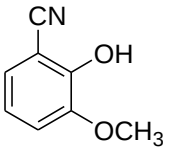


Plausible mechanism for the synthesis of nitriles from aldehydes and hydroxylamine-hydrochloride on silica-gel.

Table.Ⅱ.B.3. Synthesis of nitriles from aldehydes on silica-gel.

Entry no	Aldehydes	Time(h)	Temp(°C)	Product	Yield(%)[a]
1		4	83		87
2		4.5	110		81
3		5.5	110		82

4		5.5	83		59
5		5.5	130		54
6		5.5	105		69
7		6	130		56
8		5	130		53
9		5.5	110		62
10		5	130		64
11		4.5	100		73

12		4.5	110		82
13		4	100		86
14		4.5	100		87

[a]Isolated yield

Ⅱ.B.3. Experimental

Ⅱ.B.3.1. Chemicals

All the chemicals used for the present investigation are listed in **Table.Ⅱ.B.4.**

Table.Ⅱ.B.4.

Chemicals required for present investigation

Entry	Chemical	Source	Purity(%)
1	3-Methoxy-4-hydroxybenzaldehyde	S.D.Fine	99
2	4-hydroxybenzaldehyde	S.D.Fine	98
3	N, N-dimethyl-4-aminobenzaldehyde	Sigma-Aldrich	99
4	4-Methoxybenzaldehyde	Sigma-Aldrich	98
5	3-Nitrobenzaldehyde	LOBA Chemie	98
6	2-Chlorobenzaldehyde	S.D.Fine	97
7	Cinnamaldehyde	Sigma-Aldrich	98

8	Heptaldehyde	Spectrochem	97
9	4-Chlorobenzaldehyde	S.D.Fine	98
10	4-Nitrobenzaldehyde	LOBA Chemie	99
11	Benzaldehyde	Sigma-Aldrich	98
12	2-Hydroxy benzaldehyde	S.D.Fine	99
13	3-Methoxybenzaldehyde	Chemical Book	97
14	2-Hydroxy-3-methoxybenzaldehyde	ACROS	99
15	Hydroxylamine hydrochloride	Fisher Scientific	96
16	Sodium sulphate anhydrous	SRL	99.5
17	Petroleum ether	Thomas Baker	98
18	Ethyl acetate	Thomas Baker	99
19	Silica gel 60-120 mesh	SRL	-
20	Silica gel for TLC	SRL	-
21	Potassium bromide for IR	Merck	99
22	$CDCl_3$ for NMR	ACROS	99.8
23	DMSO-d_6 for NMR	SRL	99.8

Ⅱ.B.3.2. Reaction procedure and purification

Aldehydes(1mmol) and hydroxylamine hydrochloride (1.2mmol) were mixed with silica-gel (60-120 mesh , 1g) in motor and pestle.The mixture was grinded thoroughly.The resulting mixture was poured into a round bottom flask (50 ml) and allowed to stir on magnetic stirrer at 100°c for required time(**Table.Ⅱ.B. 1**).The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3×15 ml) washed several times with water. The combined reaction mixture was dried over anhydrous Na_2SO_4, then the solution was made concentrated and purified by column chromatography on silica gel(60-120 mesh using petroleum

ether/ethylacetate as eluent to yield pure nitrile. The desired isolated products were characterized by IR,[1] H NMR and ^{13}C NMR spectroscopy.

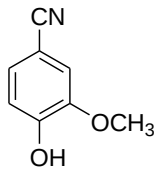
Ⅱ.B.3.3. Spectroscopic measurements

IR spectra was recorded on KBr disks and nujol on perkin Elmer FT IR spectrometer. ^{1}H and ^{13}C NMR were recorded on 300, 500 and 75 MHz Bruker Avance spectrometer using TMS as internal standard.

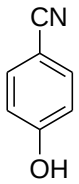
Ⅱ.B.4. Conclusion

In conclusion, the author has explored a very facile one-pot transformation of nitrile from aldehyde (1mmol), hydroxylamine hydrochloride (1.2mmol), silica gel (1gm).The main advantage of this protocol is, other groups present in the aldehydes remain unaffected and both aliphatic and aromatic aldehydes are subject to this transformation. Besides this, low cost, solvent- free, environmental friendly and simple work-up process are the added advantage of this methodology.

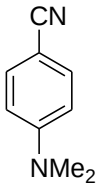
Ⅱ.B.5. Characterization data

1. 

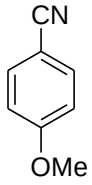
4-Hydroxy-3-methoxy-benzonitrile : IR (cm^{-1}, KBr): 3388 (-OH), 2227 (-CN), 1605, 1591, 1517, 1028, 819, 616. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 3.93 (s, 3H), 6.1 (s, 1H), 6.96 (d, 1H, J=10 Hz), 7.08 (d, 1H, J=1.5 Hz), 7.22-7.26 (m, 1H) ppm. ^{13}C NMR (75 MHz,): δ, 56.4, 103.3, 113.7, 115.2, 119.2, 127, 146.6, 149.9 ppm

2. 

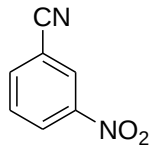
4-Hydroxy-benzonitrile: IR (cm^{-1}, KBr): 3292 (-OH), 2234 (-CN), 1613, 1586, 1509, 1285, 1167, 838,702. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 6.14 (s, 1H), 6.91 (d, 2H, J=15 Hz), 7.55 (d, 2H, J=15.5 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 103.4, 116.4, 119.2, 134.2, 159.9 ppm

3. 

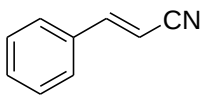
4-Dimethylamino-benzonitrile: IR (cm^{-1}, KBr): 2909, 2211 (-CN), 1608, 1527, 1371, 1173, 818. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 39.9, 97.4, 111.4, 120.6, 133.4, 152.5 ppm. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 3.04 (s, 6H), 6.69 (d, 2H, J=15 Hz), 7.48, (d, 2H, J=15 Hz) ppm.

4. 

4-Methoxy-benzonitrile: IR (cm^{-1}, KBr): 2942, 2218 (-CN), 1606, 1509, 1305, 1258, 1177, 1024, 830, 683. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 3.85 (s, 3H), 6.94 (d, 2H, J=9 Hz), 7.58 (d, 2H, J=9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 55.5, 103.9, 114.7, 119.2, 133.9, 162.8 ppm.

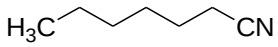
5. 

3-nitro-benzonitrile: IR (cm^{-1}, KBr): 3080, 2238 (-CN), 1618, 1534, 1356, 1102, 735. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 7.71-7.76 (m, 1H), 7.98-8.01 (m, 1H), 8.46-8.5 (m, 1H), 8.53-8.84 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 114.2, 116.5, 127.1, 127.3, 127.6, 130.6, 137.6 ppm

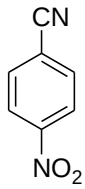
6. 

Cinnamonitrile

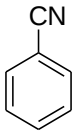
IR (cm^{-1}, neat): 2925, 2216 (-CN), 1448, 1622. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 5.85-5.95 (d, 1H, J=16.7 Hz), 7.26-7.68 (m, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 96.3, 118.1, 127.7, 128.8, 131.2, 133.4, 150.6 ppm

7. 

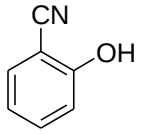
Heptanenitrile: IR (cm^{-1}, neat): 2926, 2246 (-CN), 1453, 1182. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 0.89-2.47 (m, 13H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 14, 14.2, 22.6, 23.4, 25.8, 32.2, 119.5 ppm

8. 

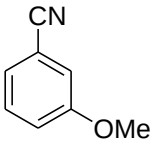
4-nitro-benzonitrile: IR (cm^{-1}, KBr): 3107, 2233 (-CN), 1602, 1526, 1349, 1295, 1106, 860, 682. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 7.88 (d, 2H, J=15 Hz), 8.35 (d, 2H, J=15 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 116.7, 118.3, 124.3, 133.4, 150 ppm

9. 

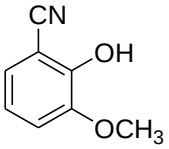
Benzonitrile: IR (cm^{-1}, KBr): 3066, 2230(-CN) , 1641, 1572. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.34-7.47 (m, 2H), 7.56-7.62 (m, 3H) ppm. ^{13}C NMR (75 MHz,): δ, 112, 118, 128, 132, 133 ppm

10. 

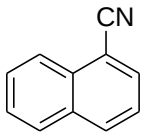
2-Hydroxy-benzonitrile: IR (cm^{-1}, KBr): 3281 (-OH), 2231 (-CN), 1605, 1505, 1361, 1236, 848, 751, 668. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 6.95-7.03 (m, 2H), 7.43-7.52 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 99.5, 116.4, 120.9, 132.9, 133.2, 134.7, 158.5ppm

11. 

3-Methoxy-benzonitrile: IR (cm^{-1}, KBr): 2943, 2230 (-CN), 1596, 1578, 1290, 1265, 1044, 788, 682. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 3.83 (s, 3H), 7.11-7.39 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 55.5, 113.4, 116.9, 118.7, 119.5, 124.2, 130.3, 159.4 ppm.

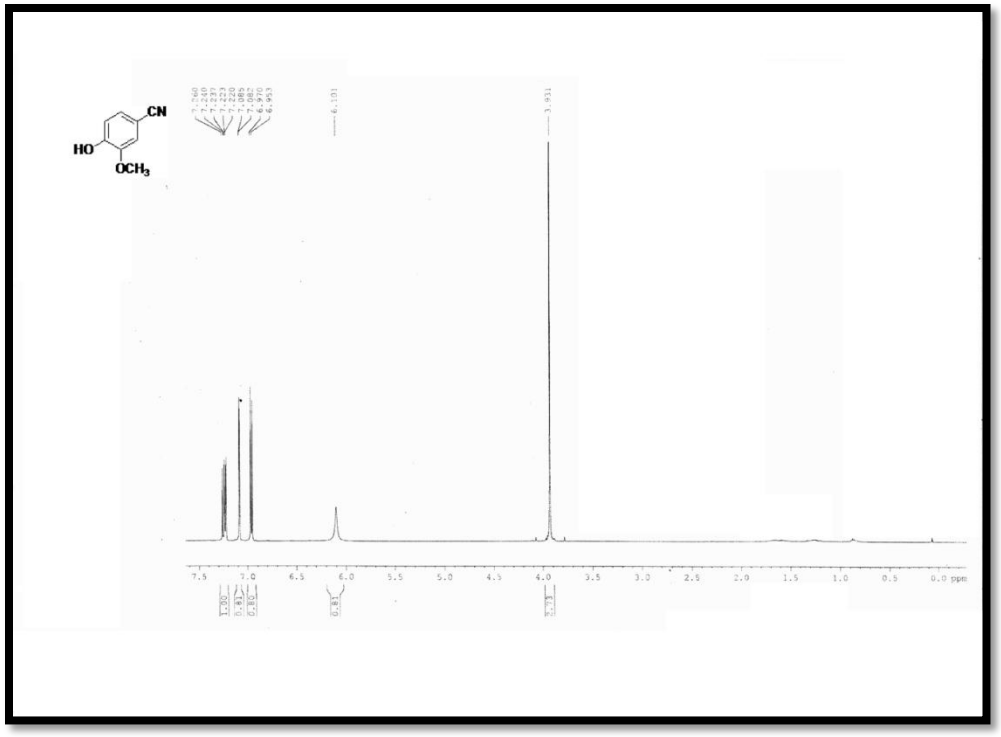
12. 

2-Hydroxy-3-methoxy-benzonitrile: IR (cm^{-1}, neat): 3351 (-OH), 2231 (-CN), 1611, 1591, 1492, 1070, 730. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 3.92 (s, 3H), 6.32 (s, 1H), 6.87-6.9 (m, 1H), 7.02-7.04 (m, 1H), 7.09 (d, 1H, J=7 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 56.3, 98.6, 114.6, 115.9, 120.4, 123.9, 146.7, 148.9 ppm

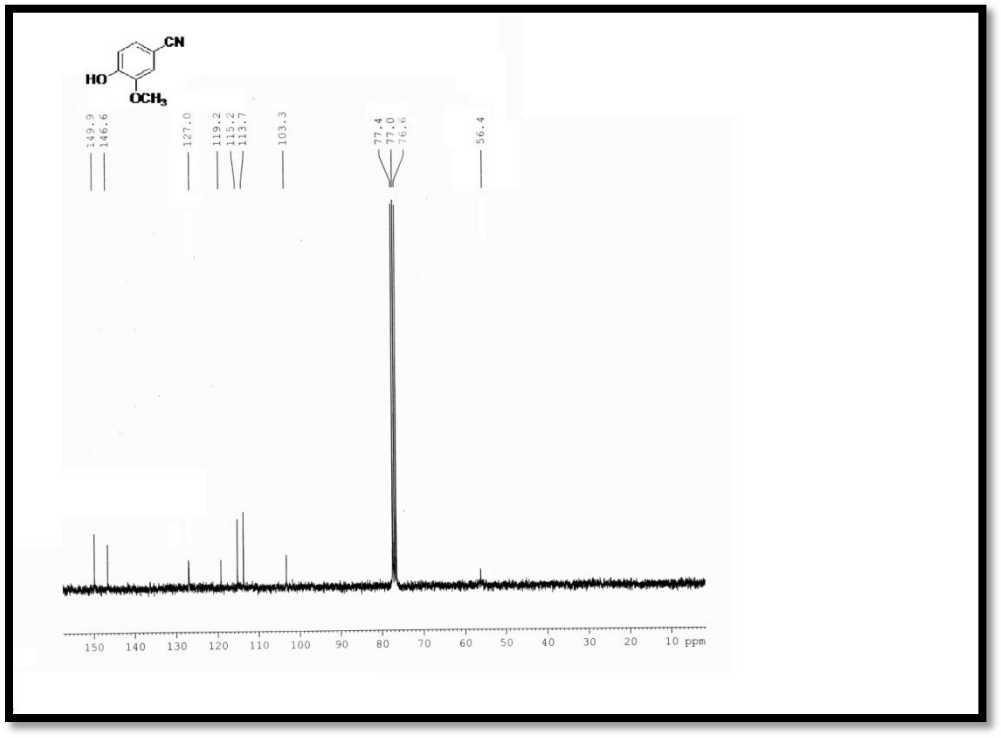
13. 

Napthalene-1-carbonitrile: IR (cm^{-1}, neat): 3061, 2222 (-CN), 1590, 1512, 1375, 1213, 801, 771. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.48-7.7 (m, 3H), 7.88-7.92 (m, 2H), 8.06 (d, 1H, J=8.1 Hz), 8.22 (d, 1H, J=8.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 110.1, 117.8, 124.9, 125.1, 127.5, 128.5, 128.6, 132.3, 132.6, 132.9, 133.2 ppm.

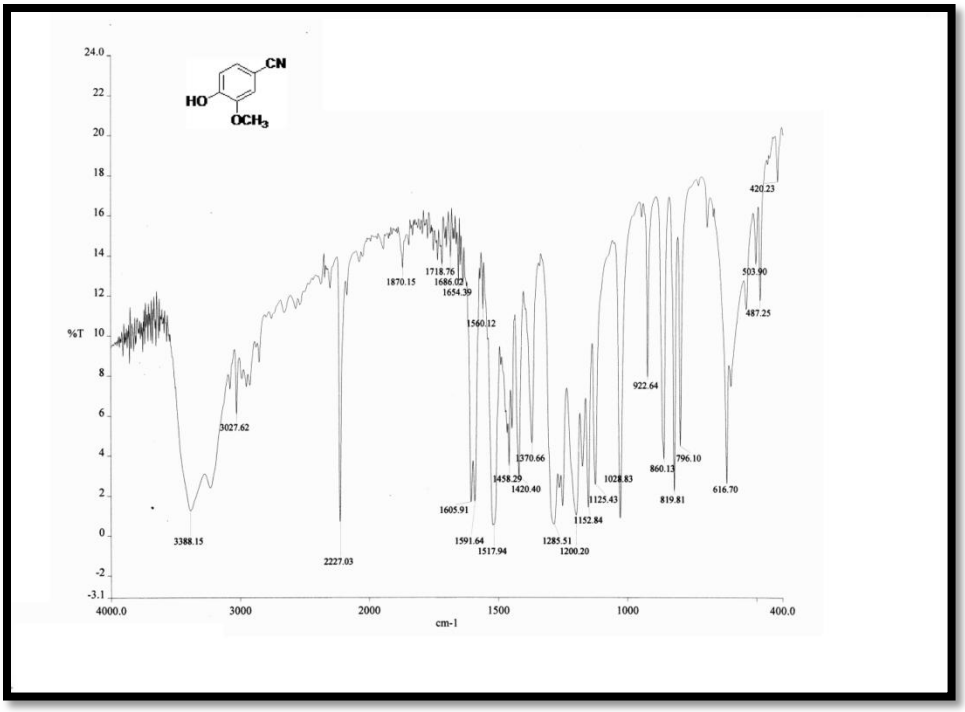
Ⅱ.B.6. Supporting spectra



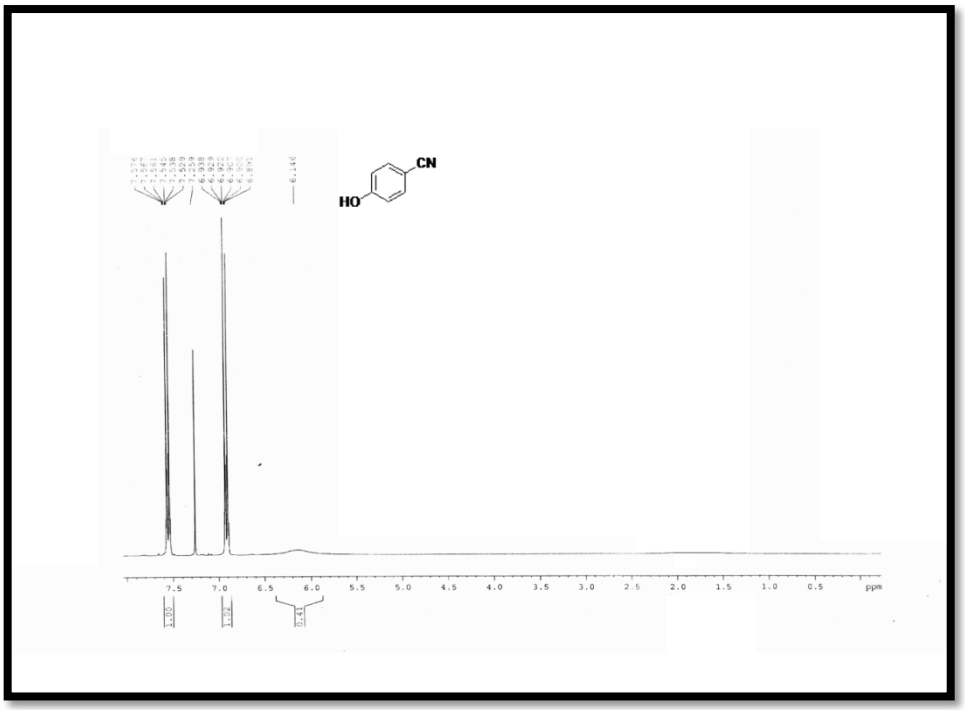
Ⅱ.B.6.1. ^{1}H NMR spectrum of 4-hydroxy-3-methoxy-benzonitrile



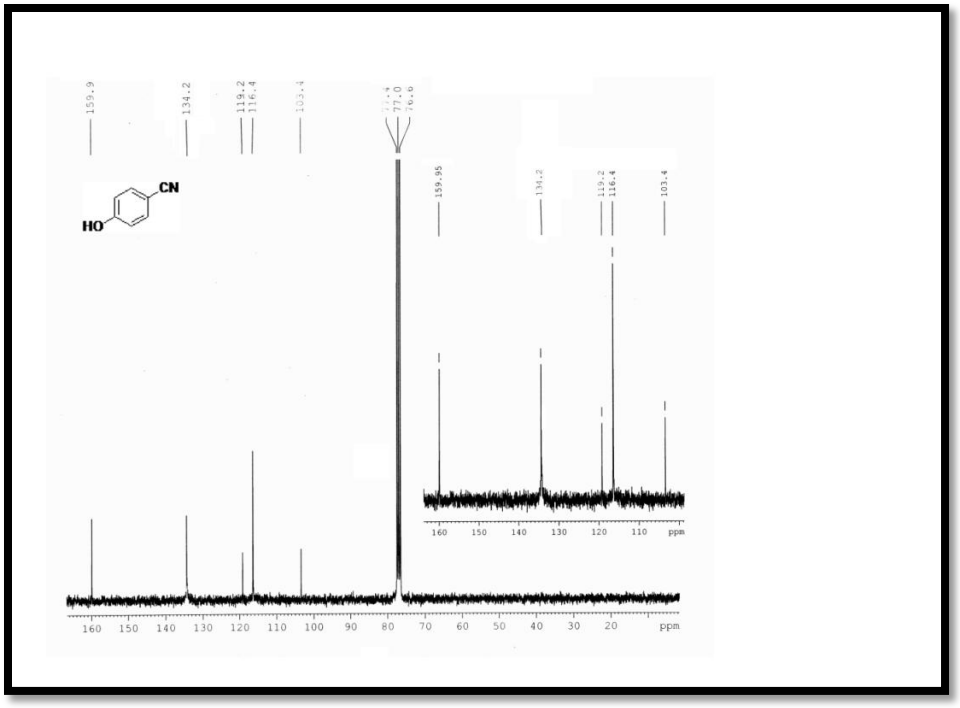
Ⅱ.B.6.2. ^{13}C NMR spectrum of 4-hydroxy-3-methoxy-benzonitrile



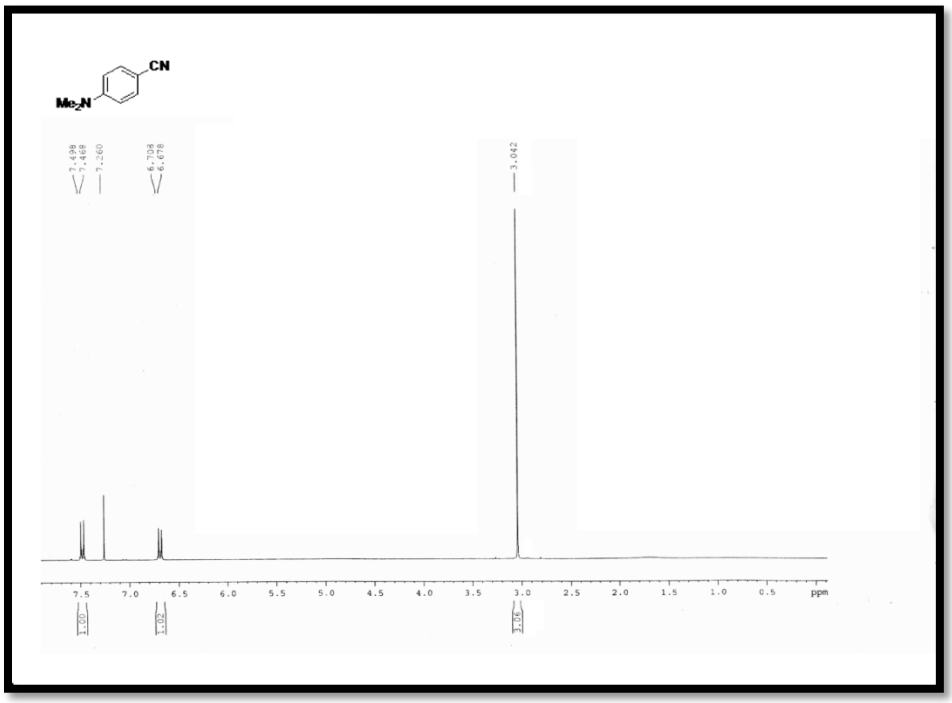
Ⅱ.B.6.3. IR spectrum of 4-hydroxy-3-methoxy-benzonitrile



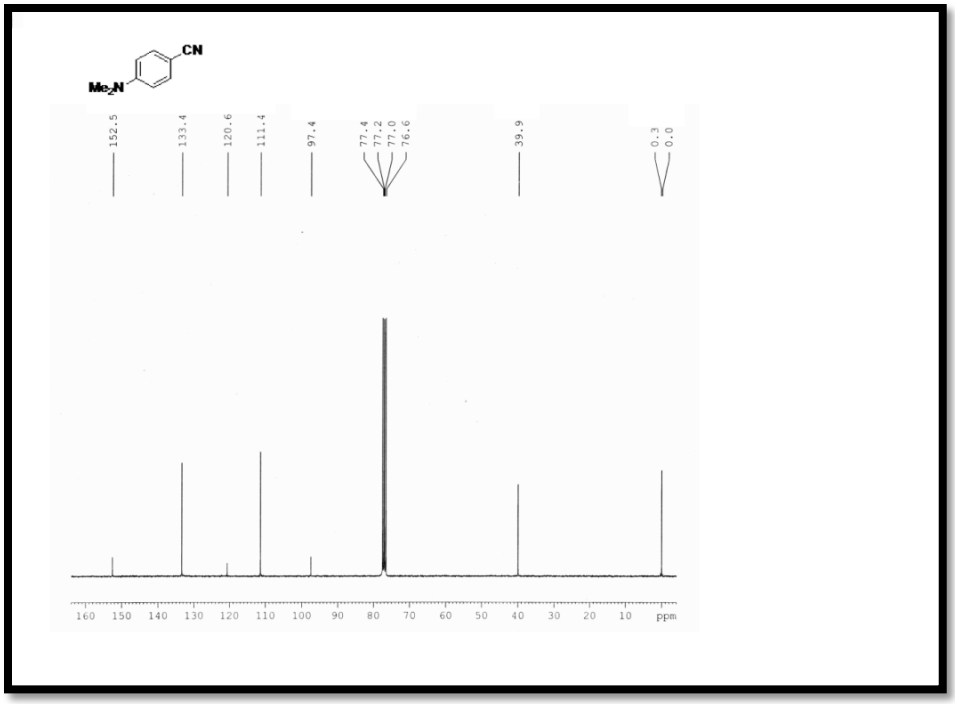
Ⅱ.B.6.4. ^{1}H NMR spectrum of 4-Hydroxy-benzonitrile



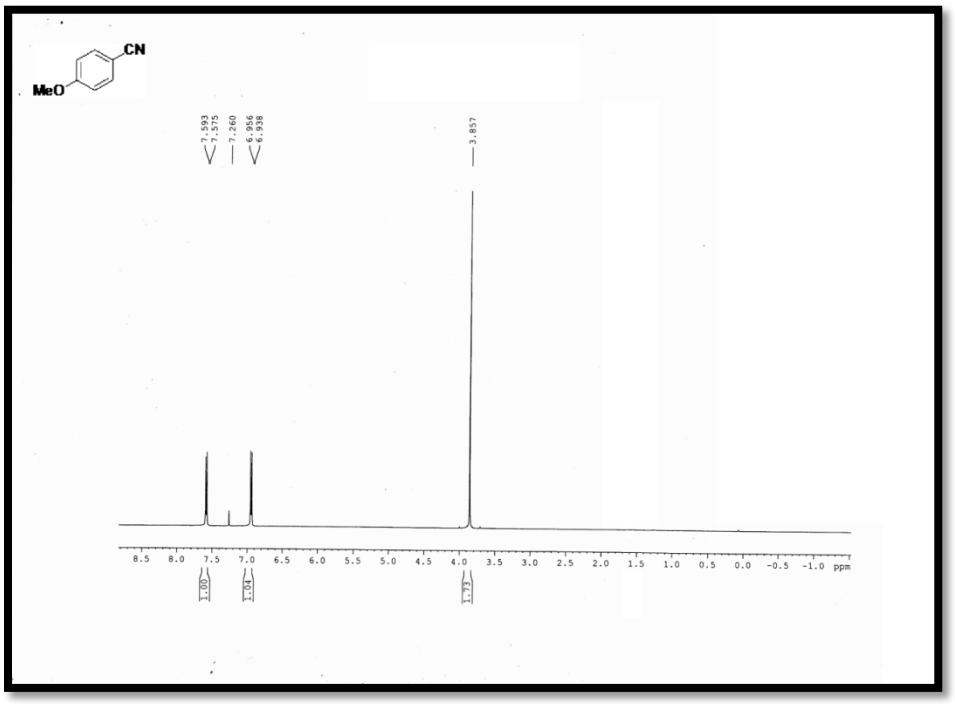
Ⅱ.B.6.5. ^{13}C NMR spectrum of 4-Hydroxy-benzonitrile



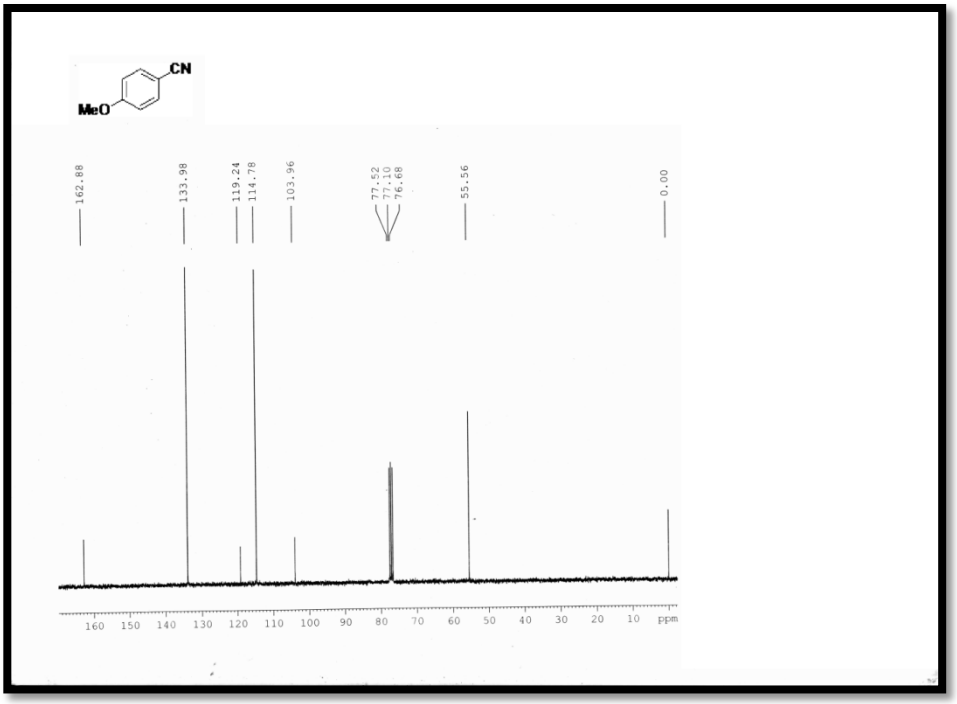
Ⅱ.B.6.6. ^{1}H NMR spectrum of 4-dimethylamino-benzonitrile



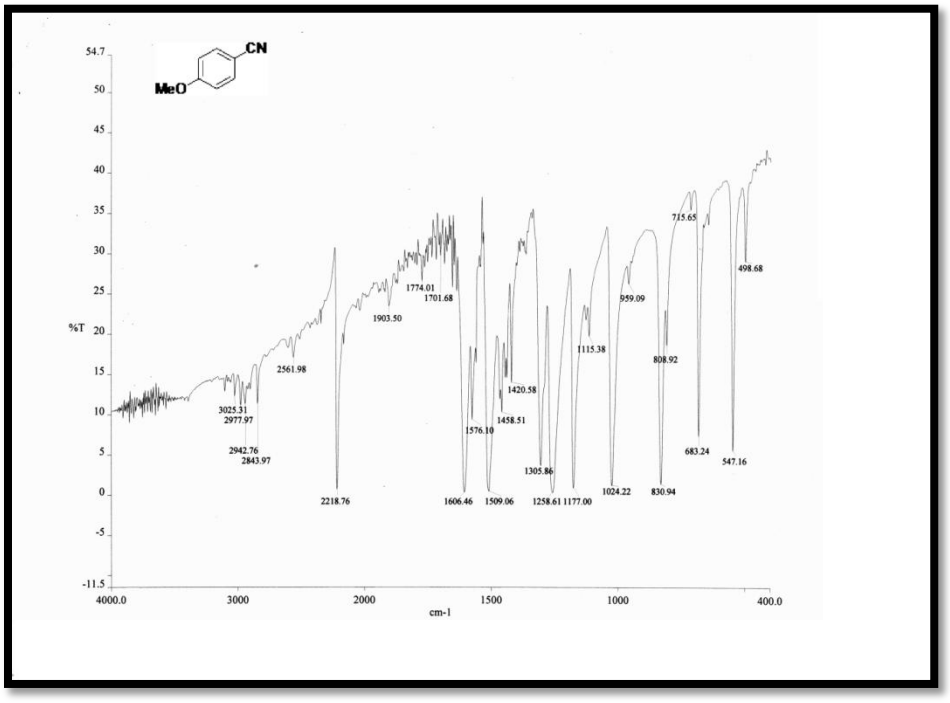
Ⅱ.B.6.7. ^{13}C NMR spectrum of 4-dimethylamino-benzonitrile



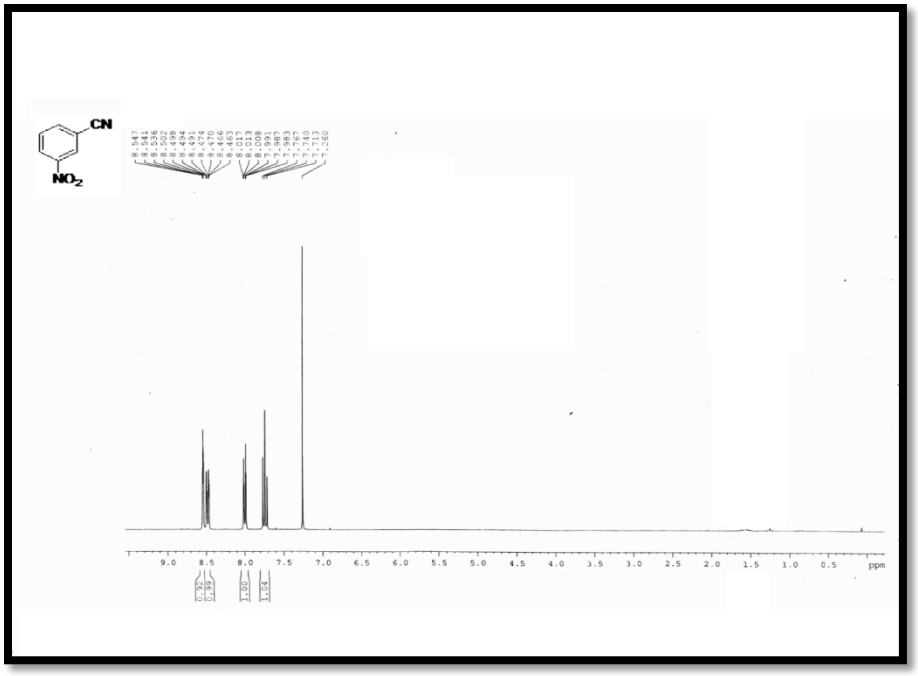
Ⅱ.B.6.8. ^{1}H NMR spectrum of 4-Methoxy-benzonitrile



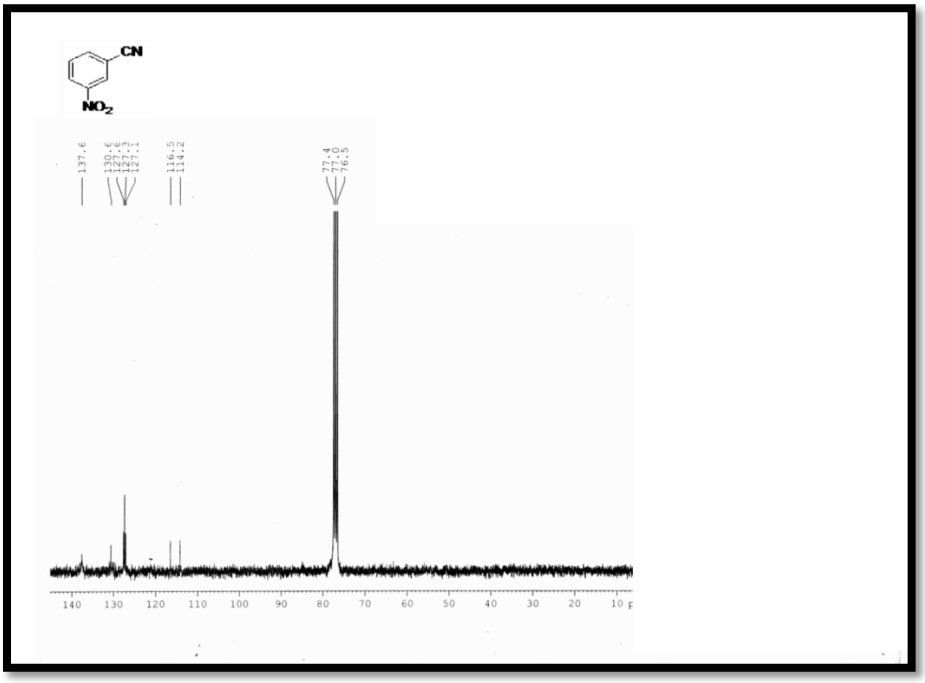
Ⅱ.B.6.9. ^{13}C NMR spectrum of 4-Methoxy-benzonitrile



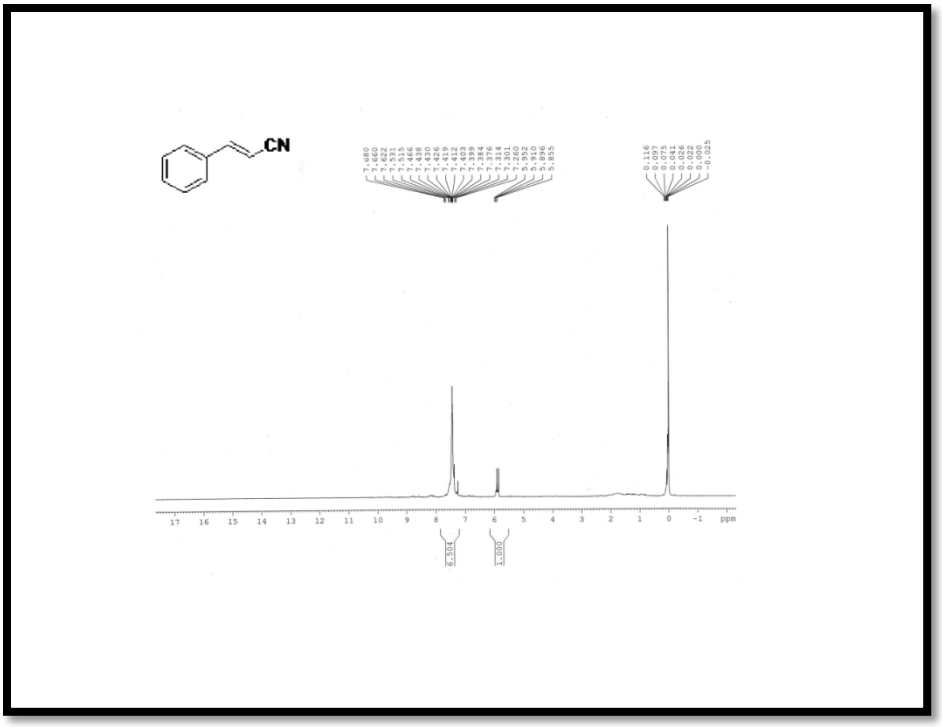
Ⅱ.B.6.10. IR spectrum of 4-Methoxy-benzonitrile



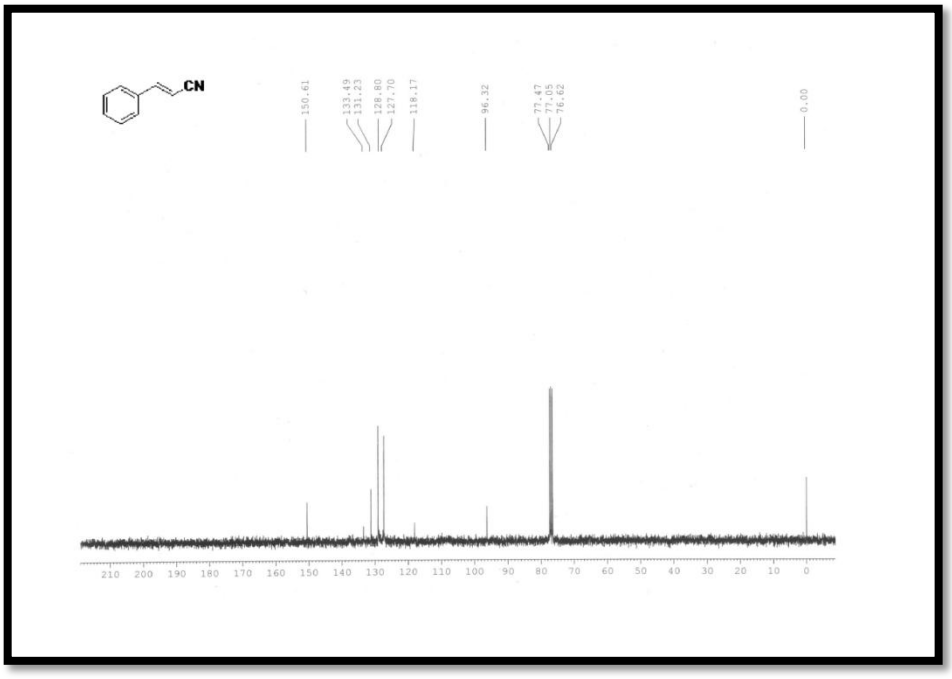
Ⅱ.B.6.11. ^{1}H spectrum of 3-nitro-benzonitrile



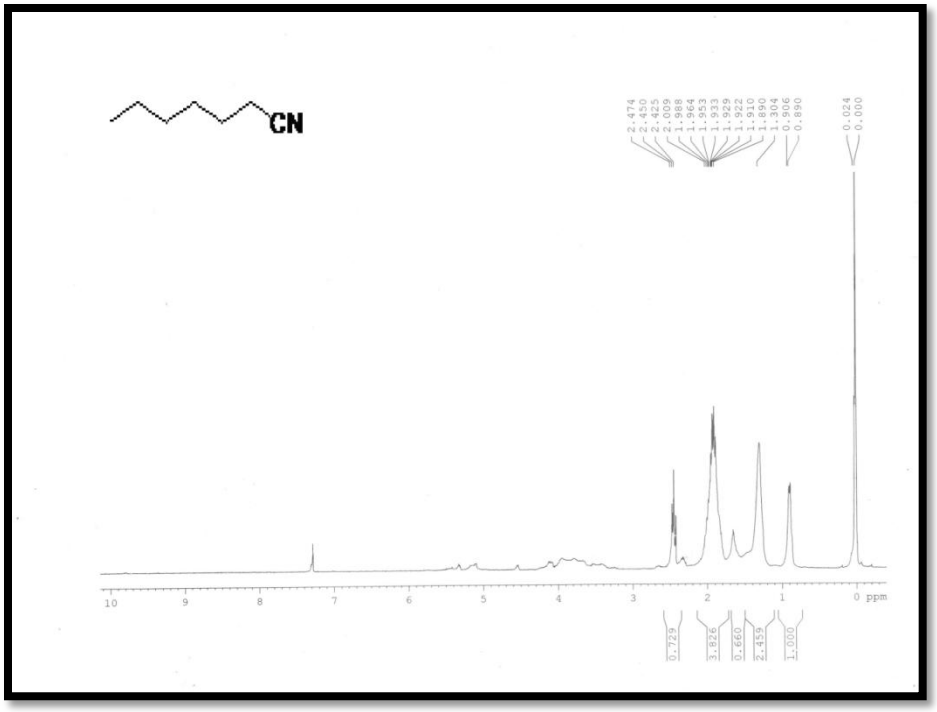
Ⅱ.B.6.12. ^{13}C NMR spectrum of 3-nitro-benzonitrile



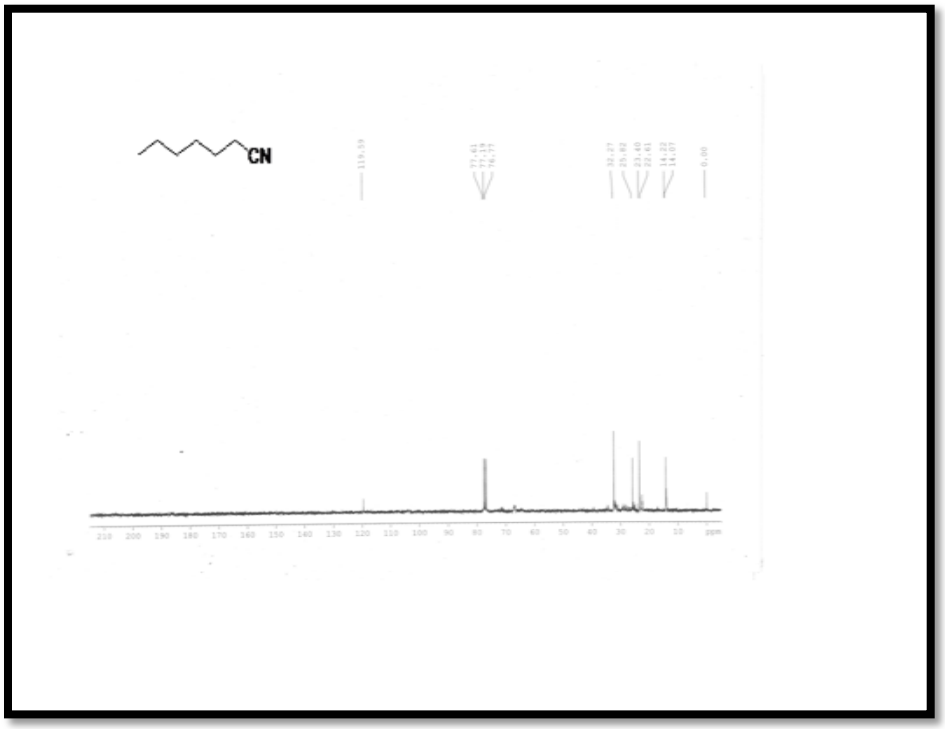
Ⅱ.B.6.13. ^{1}H NMR spectrum of cinnamonitrile



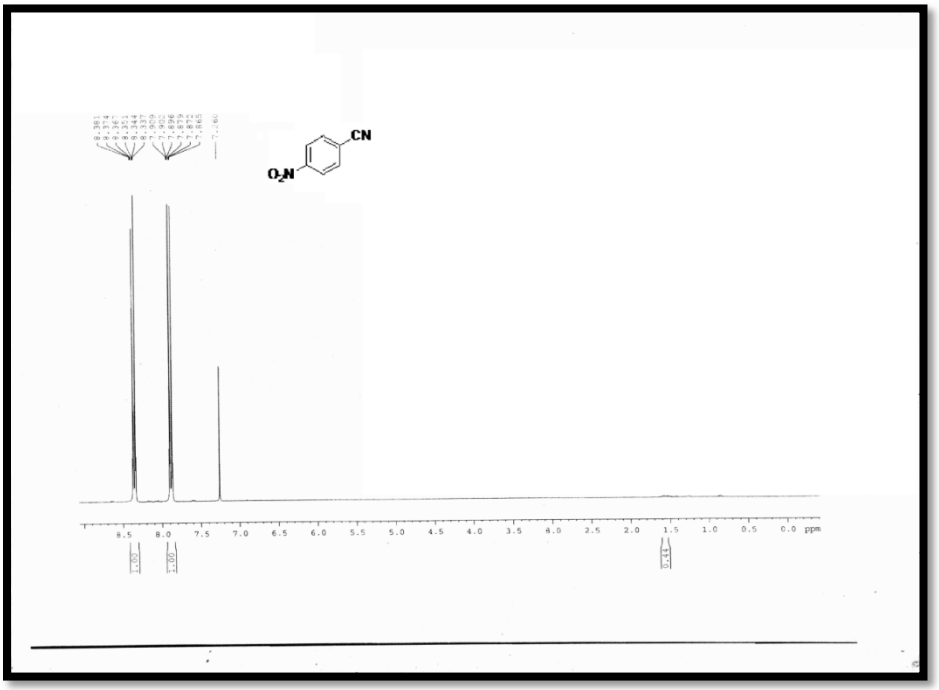
Ⅱ.B.6.14. ^{13}C NMR spectrum of cinnamonitrile



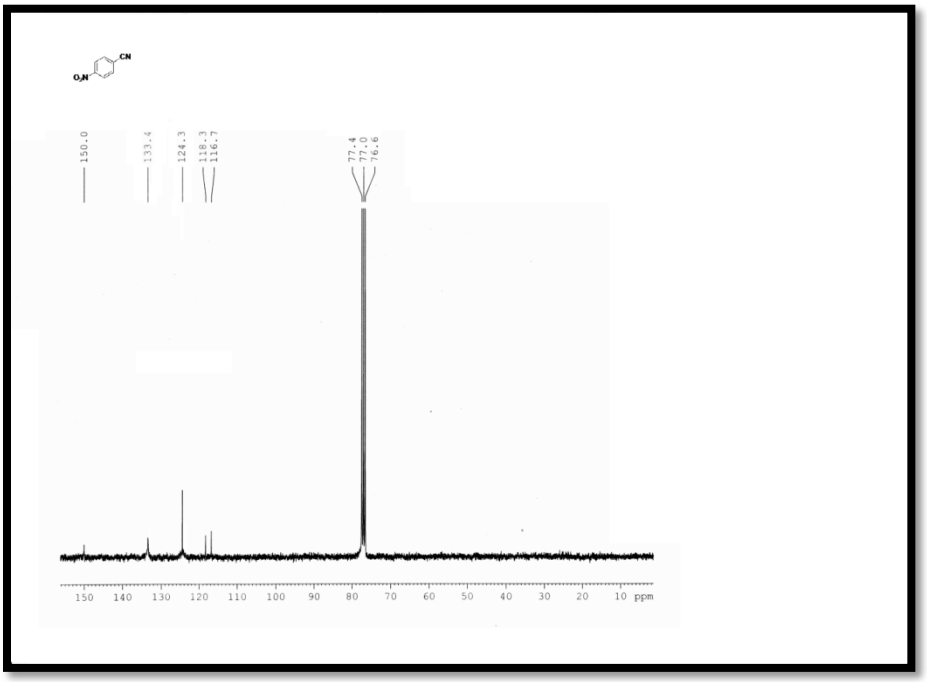
Ⅱ.B.6.15. ^{1}H spectrum of Heptanenitrile



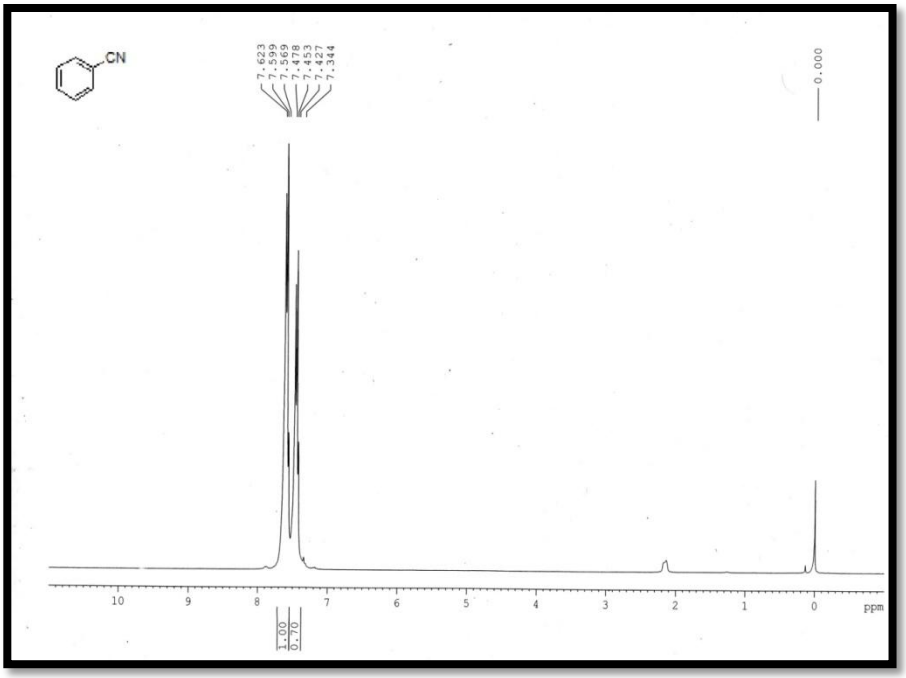
Ⅱ.B.6.16. ^{13}C spectrum of Heptanenitrile



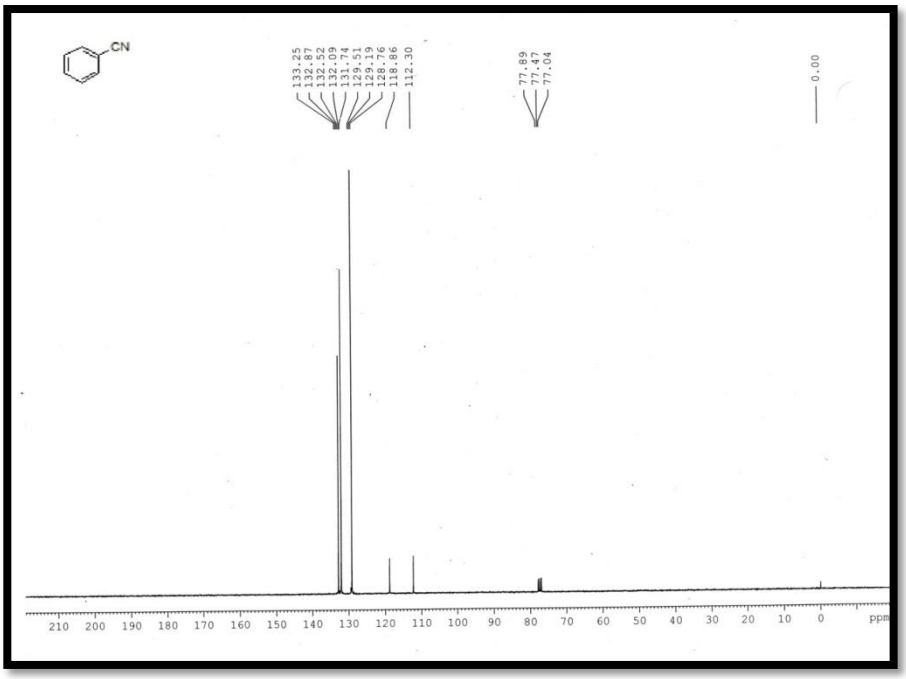
Ⅱ.B.6.17. ^{1}H spectrum of p-nitro-benzonitrile



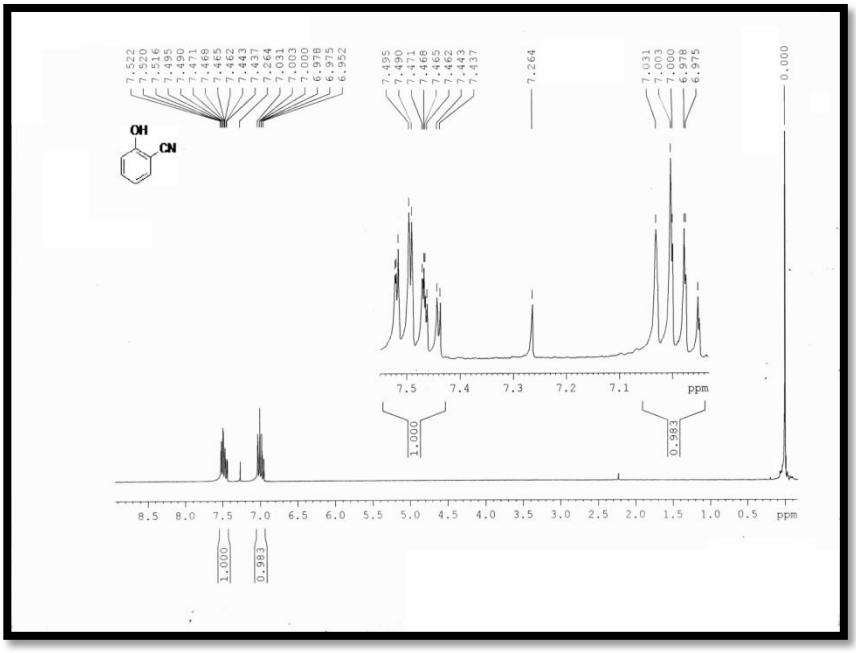
Ⅱ.B.6.18. ^{13}C spectrum of p-nitro-benzonitrile



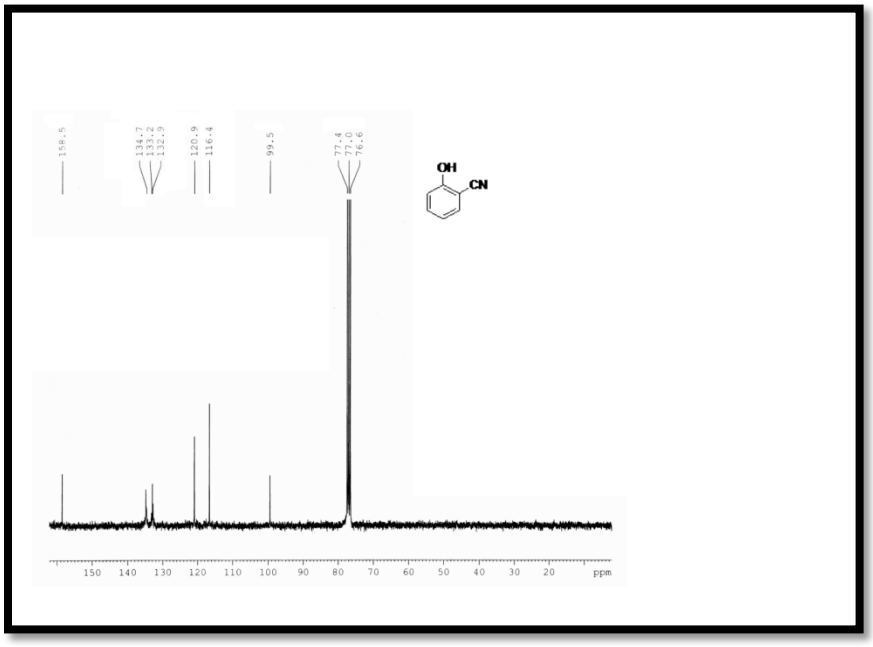
Ⅱ.B.6.19. ^{1}H spectrum of benzonitrile



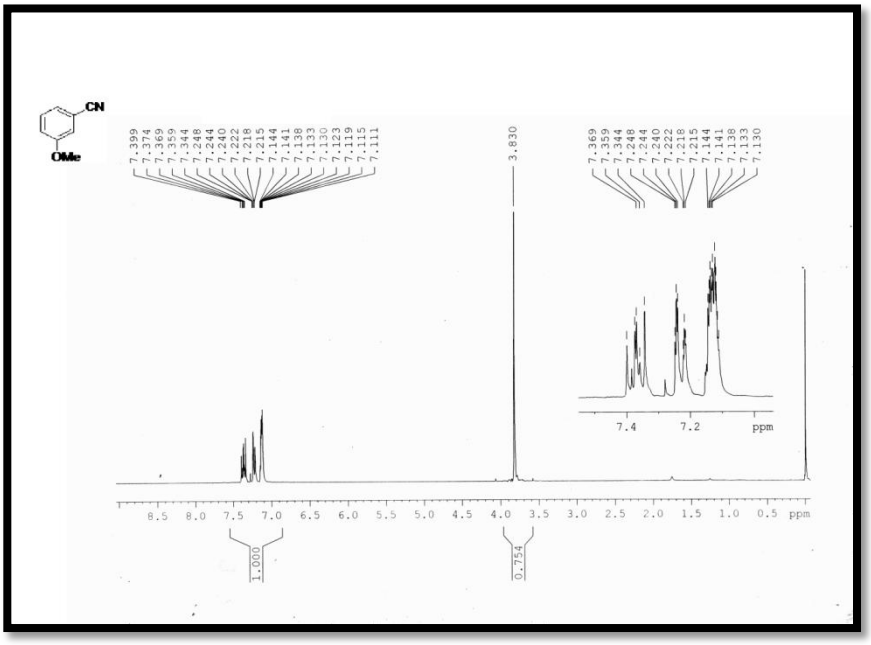
Ⅱ.B.6.20. ^{13}C NMR spectrum of benzonitrile



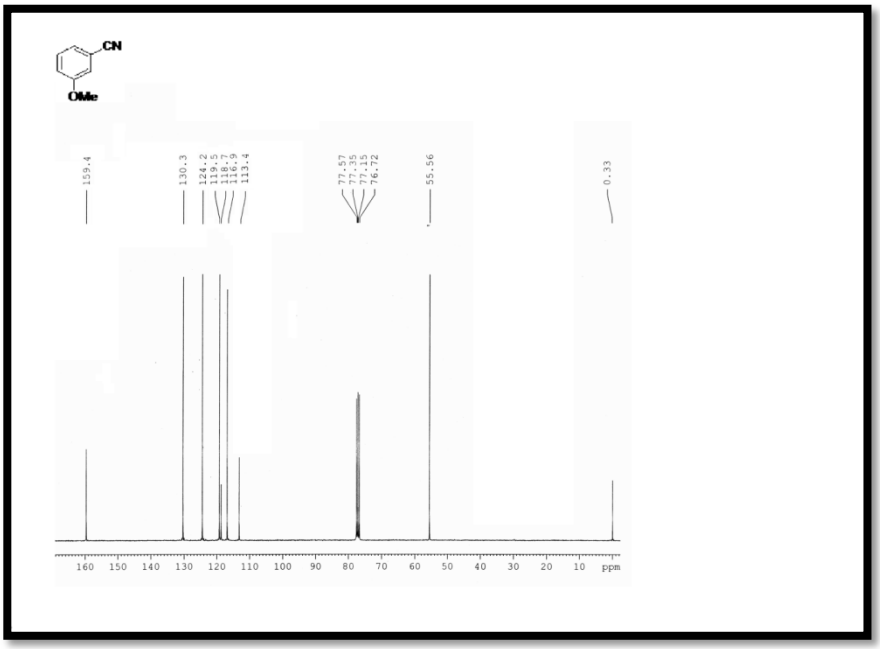
Ⅱ.B.6.21. ^{1}H NMR spectrum of 2-hydroxy benzonitrile



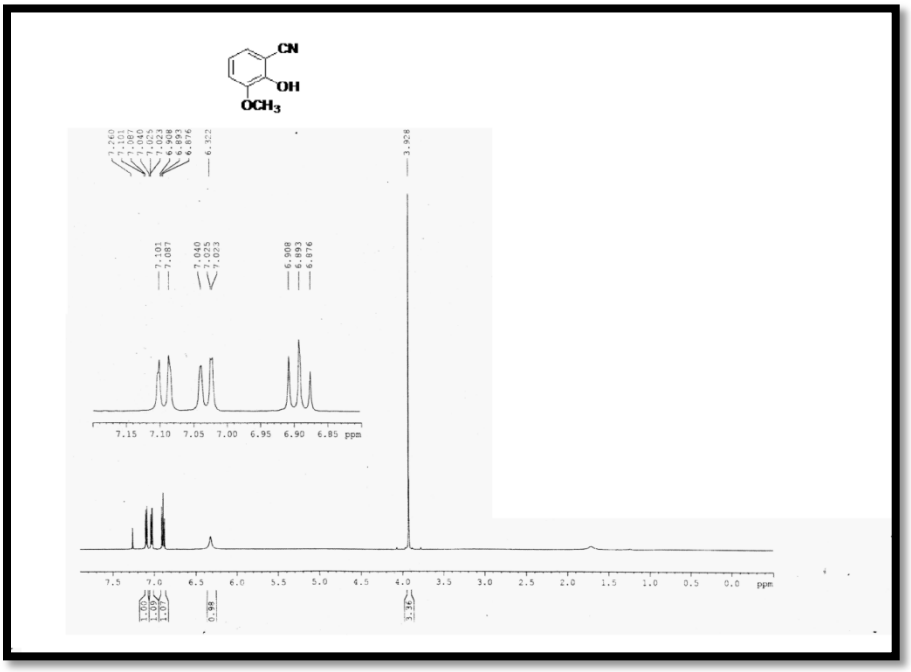
Ⅱ.B. 6.22.^{13}C NMR spectrum of 2-hydroxy benzonitrile



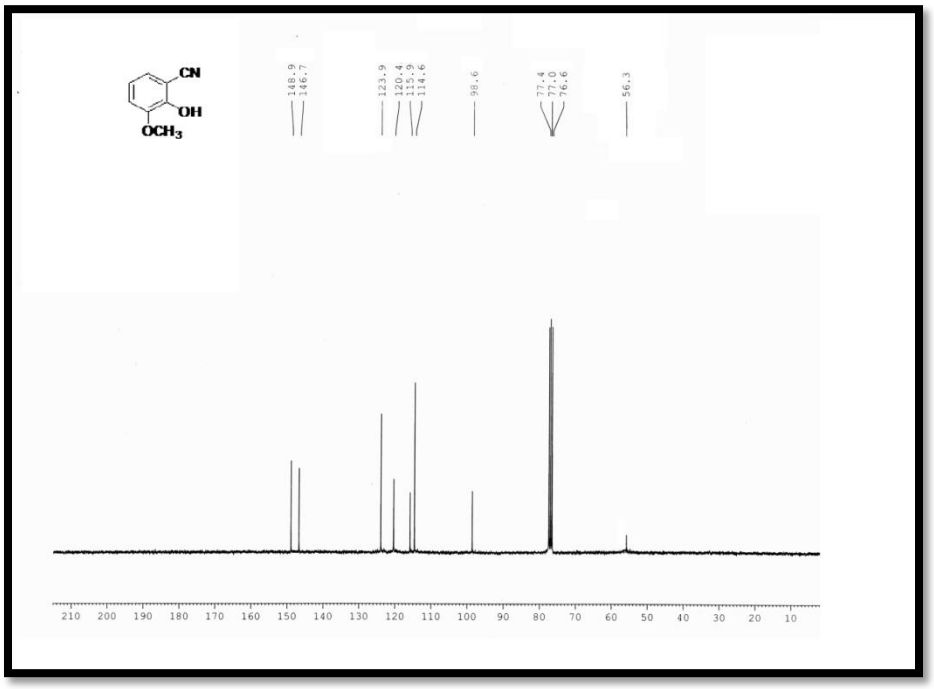
Ⅱ.B.6.23. ^{1}H NMR spectrum of 3-methoxy benzonitrile



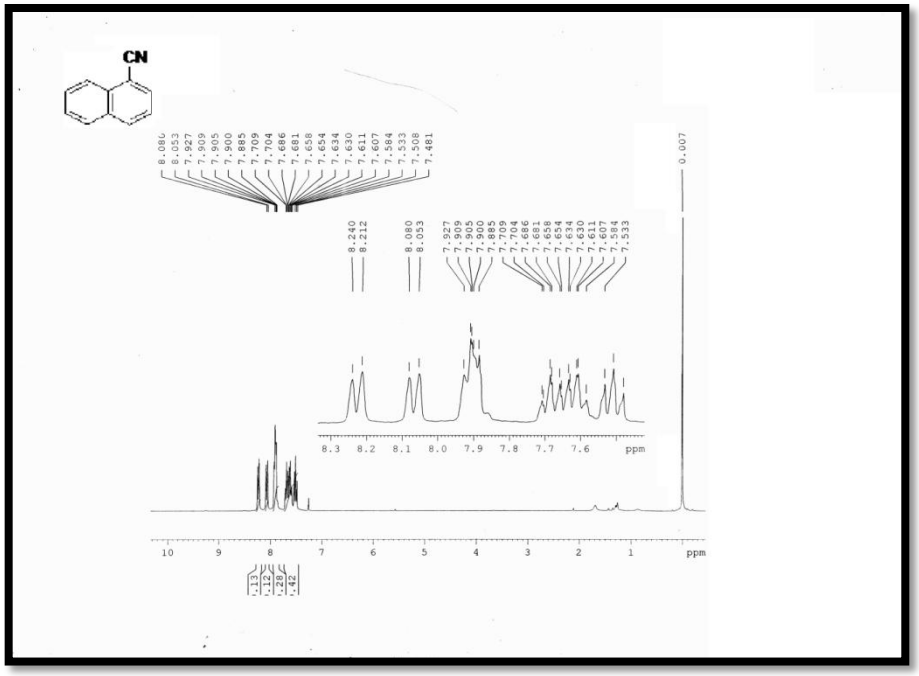
Ⅱ.B.6.24. ^{13}C NMR spectrum of 3-methoxy benzonitrile



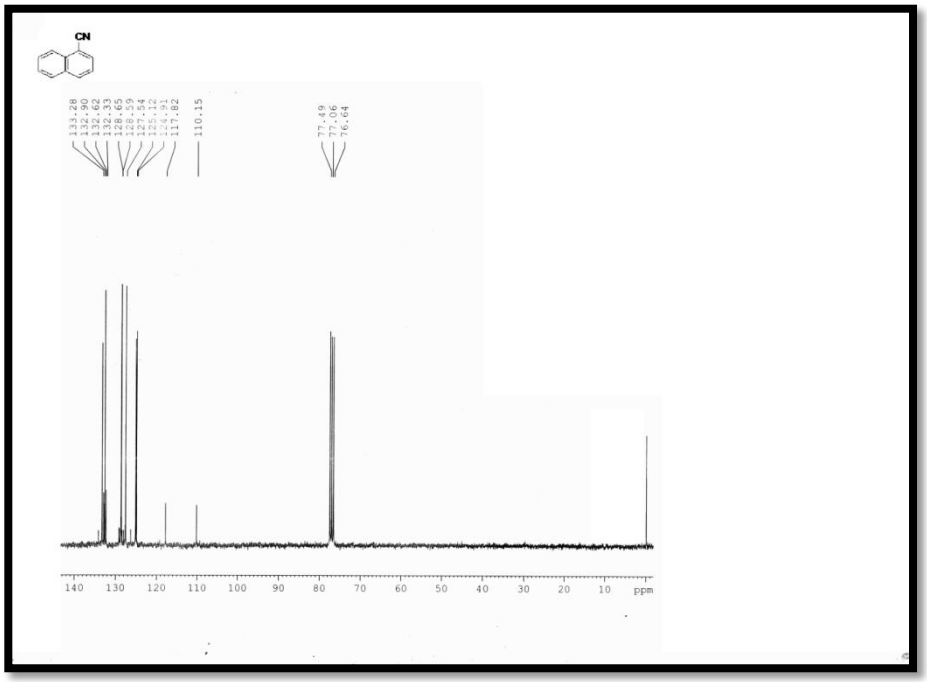
Ⅱ.B.6.25. ^{1}H NMR spectrum of 2-Hydroxy-3-methoxy-benzonitrile



Ⅱ.B.6.26. ^{13}C NMR spectrum of 2-Hydroxy-3-methoxy-benzonitrile



Ⅱ.B.6.27. ^{1}H NMR spectrum of Napthalene-1-carbonitrile



Ⅱ.B.6.28. ^{13}C NMR spectrum of Napthalene-1-carbonitrile

Ⅱ.B.7. Referrences

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CHAPTER- III

One-pot Synthesis of 5-substituted 1H-tetrazole from aldehydes Catalyzed by $TiCl_3$

CHAPTER- III

SECTION-A

III.A. A brief review on tetrazoles, synthesis and its applications

III.A.1. Tetrazole

Tetrazoles are heterocyclic compounds which have broad spectrum of biological activities such as antifungal, antiviral, antibacterial, antiulcer, anti-inflammatory, etc. 5-substituted-1H-tetrazoles can act as explosives, lipophilic spacers and finds use in material science. It is a precursor for synthesizing several nitrogen containing heterocycles used as ligands in coordination chemistry. Tetrazoles are used in medicinal chemistry as a metabolically stable carboxylic acid surrogates. It is an important intermediate for the transformation to other heterocycles. Tetrazoles are emerging to be used in pharmaceutical and material science for new application because tetrazoles are resistive to different chemical environment. 5-substituted tetrazoles have a free N-H bond, usually referred as tetrazolic acids. There is an equal tautomeric isomers of 1H- and 2H- tetrazoles. It is also known as imidoyl azides. Tetrazole is a synthetic five-membered heterocycle having four nitrogen atoms (1) (**Fig. III.A.1**). Tetrazoles are usually explosive and unknown in nature. Tetrazole (m.p.157-158∘C) is a white to pale yellow in colour, crystalline solid having a characteristic smell. It is soluble in water and alcohol.

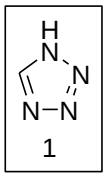


Fig. III.A.1. Tetrazole

III .A.2. Biological activities of tetrazoles

Tetrazoles are the heterocycles most used in medicinal and industrial field due to isosteric substituents for carboxylic acids.[1] It also acts as analytical reagents and plays important role in biological applications.[2, 3] 1-substituted 1H-1,2,3,4-tetrazoles were reported to be a special category because of their biological activity.[4] Tetrazoles play an important role as pharmacophores and as metabolic surrogates of carboxylic acid in several therapeutic agents which is essential for treatment of cancer, hypertension, AIDS, bacterial infection and allergies.[5,6] Well known drugs, Losartan(2) , Valsartan (3) and pamiroplast (4) are currently used as antihypertensive and 2-arylcarbapenem as antibiotic, are tetrazole structure containing compounds.[7,8]

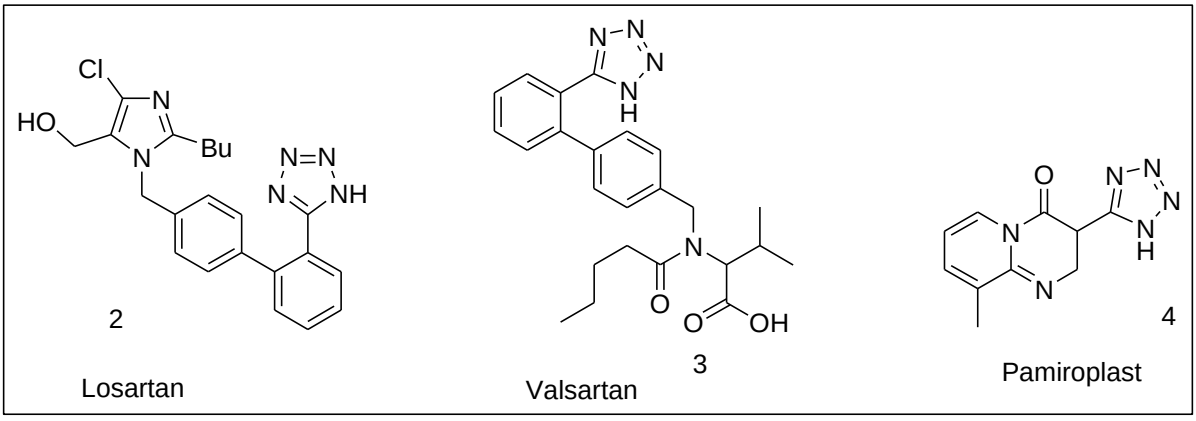


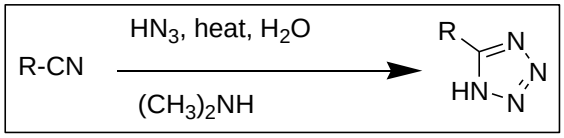
Fig. III.A.2. Example of tetrazole containing drugs

III.A.3. Application of tetrazole in organic synthesis

The tetrazole moiety shows versatile application in different field. This nitrogen rich system is mainly used in pharmaceutical[9] because there is a similarity between tetrazole and carboxylic acid group where medicinal chemist are interested. They have synthesized a lot of substituted tetrazole as important medicinal agent, e.g. a series of 5-phenyl-1-acyl-1,2,3,4-tetrazoles were synthesized through condensation of 5-phenyl-1,2,3,4-tetrazoles with different acylating agents.[10] Tetrazole plays an important role in coordination chemistry. Coordination complex with tetrazole moiety is important field of medicinal chemistry. Tetrazoles form complexes with metal ions, Cu(Ⅱ), Ni(Ⅱ), Co(Ⅱ) and Zn(Ⅱ) which acts as ligands in e.g. Cefazolin antibiotic, that shows better antibacterial activity than non coordinated one.[11] Tetrazoles are versatile intermediate which give rise to substituted tetrazoles and other 5-membered heterocyclic ring through Huisgen rearrangement.[12]

III. A.4. Classical method for the synthesis of tetrazole

Tetrazole was first prepared in 1932 by the reaction of hydrazoic acid (HN_3) with organic cyanides.[13] This process was believed to occur through concerted 1, 3-dipolar cycloaddition reaction.Subsequent work-up process provided the tetrazolic acid. (**Scheme.III.A.1**)



Scheme III. A.1. Synthesis of tetrazole by hydrazoic acid with cyanide

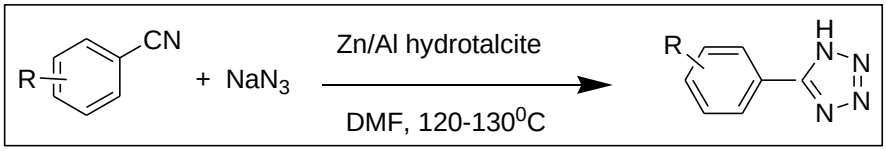
Literature study reveals that, classically, tetrazoles were synthesized by the cycloaddition of cyanides with metal azides. But due to toxic and explosive nature nature of cyanide and azides respectively, lot of catalytic methods have been introduced using different type of azides with nitriles. However, due to some drawbacks of previous methodologies, a number of new methodologies for the synthesis of tetrazoles have been developed from the combination of some different functional groups.

III.A.5. Modern methods for synthesis of tetrazole derivatives

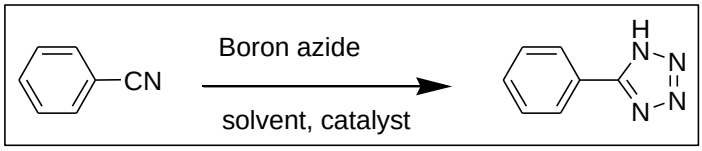
III.A.5.1. Synthesis of tetrazoles from the reaction of cyanides with azides under different catalytic conditions

To overcome the drawbacks of the classical method of synthesizing tetrazole derivatives, the development of new protocols was necessary. Use of the combination of cyanides with azides is one of the simple method for the synthesis of tetrazole derivatives. There are several catalytic process mentioned in the literature for the synthesis of tetrazole derivatives so as to minimize the drawbacks of the classical method such as Zn/Al hydrotalcite catalyzed synthesis of 5-substituted 1H-tetrazoles from the reaction of aryl nitrile and sodium azide [14] (**Scheme. III.A.2**), $CuSO_4.5H_2O$ catalyzed synthesis of 5-substituted-1H-tetrazole from the reaction of aryl or alkyl nitriles with sodium azide in DMSO,[15] $AgNO_3$ catalyzed preparation of 5-substituted-1H-tetrazole through [3+2] cycloaddition reaction of nitriles with sodium azide,[16] synthesis of 5-substituted 1H-tetrazole from the reaction of boron-azides and nitriles (**Scheme. III.A.3**.),[17] Activated Fuller's earth catalyzed synthesis of 5-aryl 1H-tetrazole from nitrile and sodium azide (**Scheme. III.A.4**.),[18] Glycerol mediated, catalyst free synthesis of 5-substituted 1H-tetrazole,[19] Zinc chloride catalyzed, solvent free synthesis of 5-substituted 1H-tetrazoles,[20] Synthesis of 1,5-disubstituted tetrazoles by palladium-catalyzed Suzuki coupling reaction (**Scheme. III.A.5**.),[21] Pb(Ⅱ) salt catalyzed synthesis of 5-substituted 1H-tetrazoles

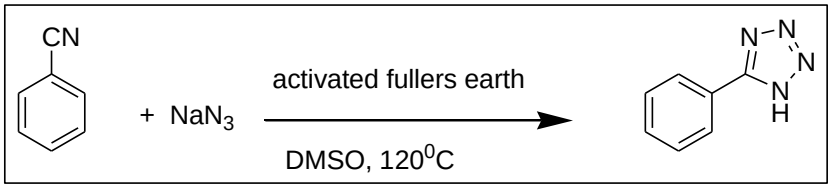
from nitriles and sodium azide,[22] Synthesis of 2-aryl-2H-tetrazoles through regioselective [3+2] cycloaddition reaction of arenediazonium salt with trimethylsilyldiazomethane (**Scheme. III.A.6**.),[23] Cyanuric chloride catalyzed, metal free synthesis of 5-substituted-1H-tetrazole,[24] Nano TiO_2/SO_4^{2-} catalyzed synthesis of 5-substituted-1H-tetrazoles,[25] Ag nanoparticle catalyzed synthesis of 5-substituted 1H-tetrazoles,[26] Ceric ammonium nitrate supported HY-zeolite catalyzed synthesis of tetrazole,[27] Silica supported lanthanum triflate catalyzed synthesis of 5-substituted-1H tetrazole (**Scheme .III.A.7**.),[28] nano copper oxide catalyzed synthesis of tetrazoles,[29] $CuFe_2O_4$ nanoparticles catalyzed synthesis of 5-substituted 1H-tetrazoles,[30] $FeCl_3$-SiO_2 catalyzed synthesis of 5-substituted 1H-tetrazoles through [2+3] cycloaddition of nitriles with sodium azide,[31] copper catalyzed synthesis of 5-substituted 1H-tetrazoles through cycloaddition of nitriles with trimethylsilyl azide,[32] (**Scheme. III.A.8**.), nano-$TiCl_4.SiO_2$ catalyzed synthesis of 5-substituted 1H-tetrazoles.[33]



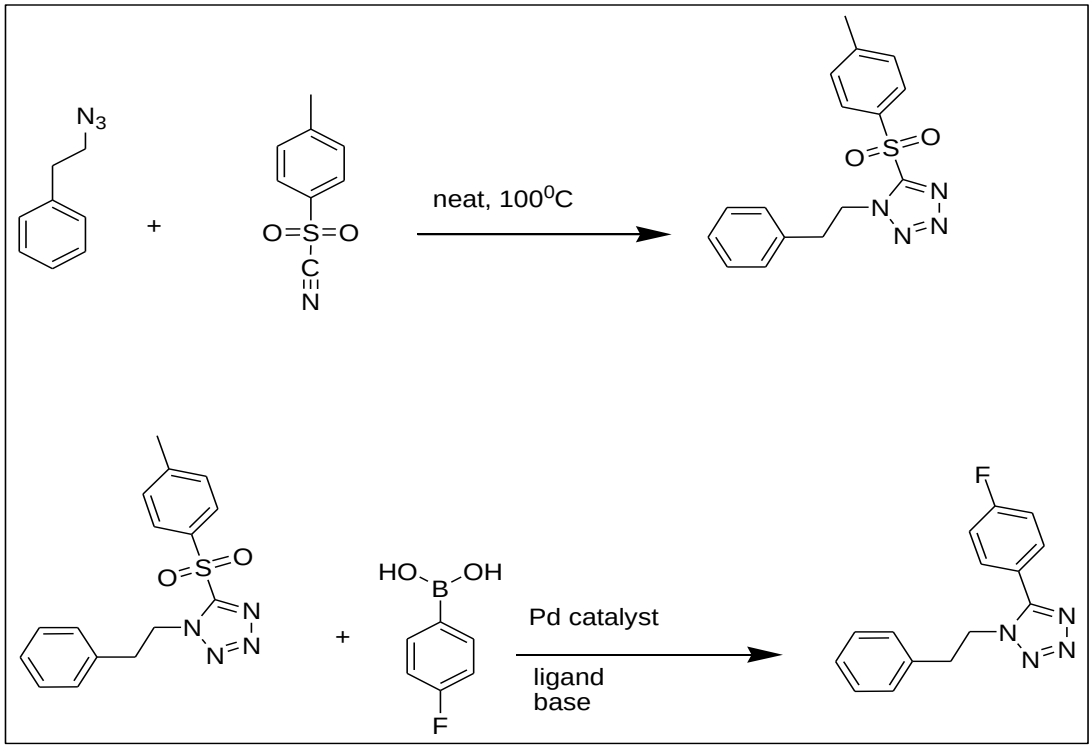
Scheme. III.A.2. Synthesis of 5-substituted 1H-tetrazole catalyzed by Zn/Al hydrotalcite



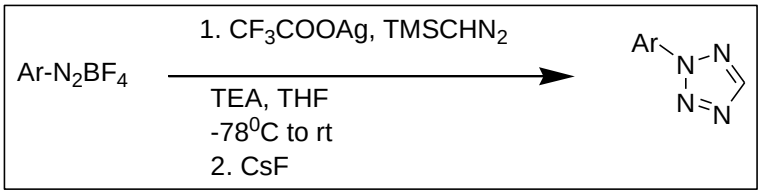
Scheme. III.A.3. Synthesis of tetrazoles catalyzed by boron azide



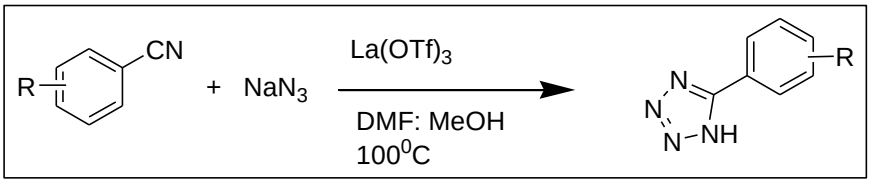
Scheme.III.A.4. Synthesis of 5-aryl-1H-tetrazole catalyzed by Activated Fuller's earth



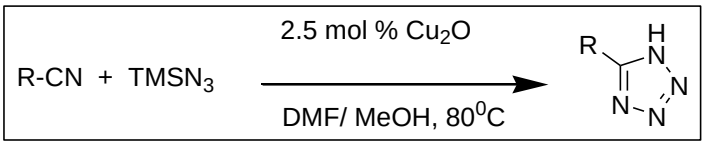
Scheme. III. A.5. Synthesis of 1, 5-substituted tetrazole by Pd catalyzed Suzuki coupling



Scheme. III.A.6. Synthesis of 2-aryl tetrazole by aryl diazonium salt



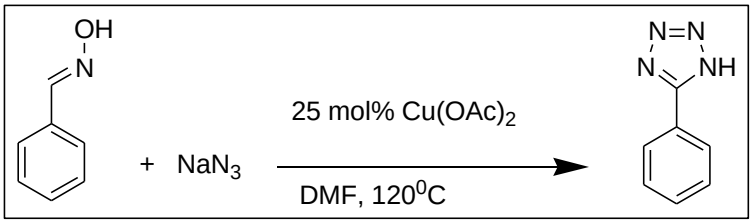
Scheme. III.A.7. Synthesis of 5-substituted tetrazole catalyzed by $La(OTf)_3$



Scheme. III.A.8. Synthesis of tetrazoles by trimethylsilylazide

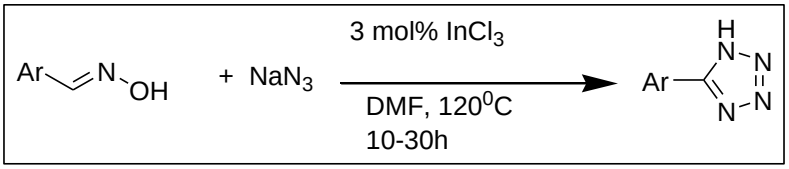
III.A.5.2. Synthesis of tetrazole derivatives from the combination of oxime and azides

Generally tetrazoles are prepared by using toxic and expensive aryl nitriles as precursors. Therefore nitriles are replaced by oximes. J.M.Nagarkar et.al.[34] synthesized 5-substituted 1H-tetrazole from the reaction of oxime with sodium azide (**Scheme. III.A.9**.)



Scheme. III.A.9. Synthesis of 5-substituted 1H-tetrazole from oxime, catalyzed by $Cu(OAc)_2$

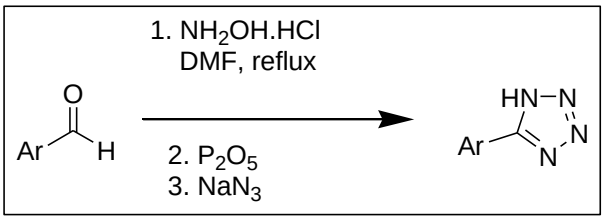
S.D.Guggilapu et.al.[35] synthesized 5-substituted 1H-tetrazole derivatives from the reaction of oxime and sodium azide catalyzed by Indium(Ⅲ) chloride, a lewis acid catalyst (**Scheme. III.A.10**.)



Scheme. III.A.10. Synthesis of 5-substituted 1H-tetrazole from oxime, catalyzed by $InCl_3$

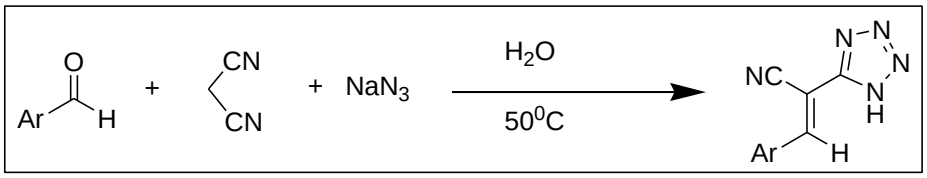
III.A.5.3. Synthesis of tetrazole derivatives from aldehydes

K.M.Khan et.al.[36] synthesized tetrazole derivatives from the reaction of substituted benzadehyde with sodium azide in presence of hydroxylamine hydrochloride and P_2O_5 in DMF under reflux condition (**Scheme. III.A.11**.)



Scheme. III.A.11. Synthesis of tetrazole derivatives from aldehyde, hydroxylamine hydrochloride, sodium azide in presence of P_2O_5

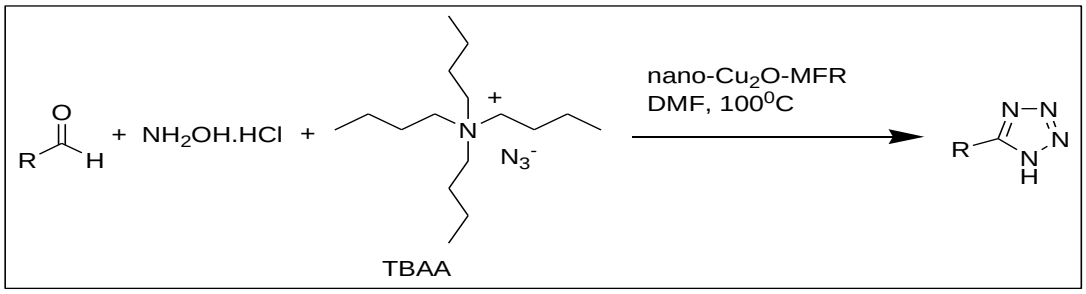
Z.N.Tisseh et.al.[37] synthesized 5-substituted 1H-tetrazole in aqueous medium without catalyst, from the reaction of aldehyde with malononitrile and sodium azide (**Scheme.Ⅲ.A.12**.). The reaction was diastereoselective.



Scheme .III.A.12. Synthesis of 5-substituted 1H-tetrazole from aldehyde, malononitrile and sodium azide in aqueous medium

S. Behrouz (2017)[38] synthesized 5-substituted 1H-tetrazole derivatives from aldehydes catalyzed by doped nano-sized Cu_2O on melamine-formaldehyde resin (nano-Cu_2O-MFR). In this three-

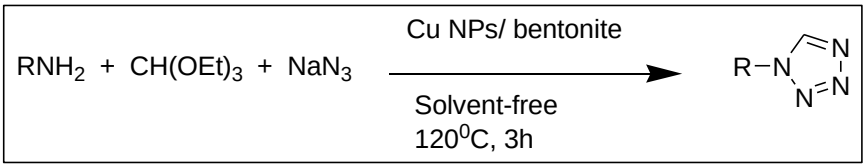
component method structurally diverse aldehydes are reacted with hydroxylamine hydrochloride and tetrabutylammonium azide (TBAA) as a source of azide, catalyzed by nano-Cu_2O-MFR(**Scheme. III.A.13**.)



Scheme.III.A.13. Synthesis of 5-substituted 1H-tetrazole from aldehydes, hydroxylamine hydrochloride and TBAA in presence of nano-Cu_2O-MFR

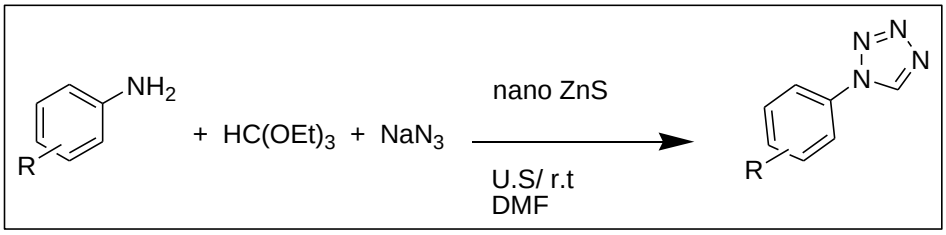
III.A.5.4. Synthesis of tetrazole derivatives from amine, hydrazides, isocyanides and primary alcohols

A.R.Vartooni et.al.[39] synthesized 1-substituted 1H-1,2,3,4-tetrazoles from amine, NaN_3, triethyl orthoformate catalyzed by Cu nano particles/bentonite (**Scheme.Ⅲ.A.14**.)



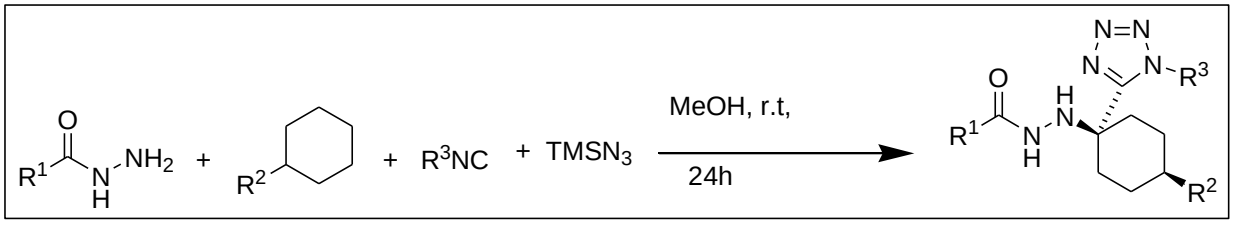
Scheme. III.A.14. Synthesis of 1-aryl-1H-1,2,3,4-tetrazole catalyzed by Cu NPs/bentonite

H.Naeimi and F.Kiani [40] synthesized tetrazoles from aryl amine and triethyl orthoformate under ultra sound irradiation catalyzed by Zinc sulfide nanoparticles (**Scheme. III. A.15**.)



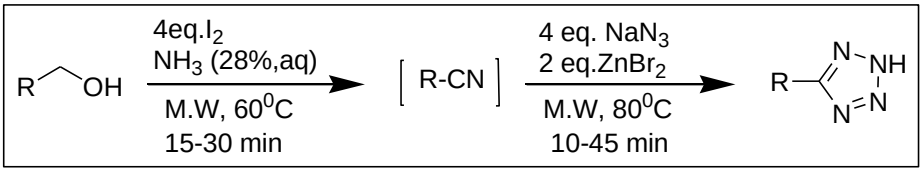
Scheme. III.A.15. Synthesis of 1-substituted 1H-1,2,3,4-tetrazoles by ZnS NPs under ultrasound irradiation

S.Ramezanpour et.al.[41] synthesized a 1,5-disubstituted diastereoselective α-hydrazino tetrazoles through four-component reaction using diverse cyclic ketones, hydrazides, isocyanides and trimethylsilyl azide at room temperature (**Scheme. III.A.16**.)



Scheme. III.A.16. Synthesis of 1, 5-disubstituted α-hydrazino tetrazoles by four-component reaction

J.J.Shie and J.M.Fang [42] explored the microwave- assisted direct transformation of primary alcohol to tetrazole derivatives in aqueous medium (**Scheme. III.A.17**.)



Scheme. III.A.17. One-pot transformation of primary alcohol into tetrazole derivatives

III.A.6. Conclusion

Tetrazoles are associated with several pharmaceutical as well as industrial applications and people have devoted themselves to develop new methodologies for the synthesis of tetrazole derivatives so that the shortcomings of the classical methods can be minimized. Literature study reveals that there are several catalytic synthetic methodologies for the preparation of tetrazole derivatives. But most of the reported processes are not so simple and cost-efficient. Based on these facts, author realized to develop a simple, cost-efficient and straight forward method for the synthesis of tetrazole derivatives, which are of the interest of sustainable development.

III.A.7. References

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CHAPTER- III

SECTION-B

One-pot Synthesis of 5-substituted-1H-tetrazole from aldehydes Catalyzed by $TiCl_3$

III.B. Present Investigation

III.B.1. Background of the present investigation

Tetrazoles are a class of heterocycles which are receiving considerable attention due to wide range of applications associated with it and the literature having tetrazole chemistry are growing rapidly[1] .Tetrazoles are reported to possess a huge biological activities such as antifungal[2], antibacterial [3], analgesic[4], antiviral, anti-inflammatory, antiulcer [5], and antihypertensive activities[6].Synthetic tetrazole derivatives have also been reported to possess antidiabetic [7], anti-HIV[8] activities and used for treatment of asthma[9]. 5-substituted-1H-tetrazoles can act as lipophilic spacer and carboxylic acid surrogates[10] and used in explosives[11], function as ligands in coordination chemistry[12].In addition, some famous drugs , Pamiroplast, candesartan, valsartan, losartan, and zolarsartan [13] contain tetrazolyl moieties. Traditional synthesis of 5-substituted 1H-tetrazole has been reported to proceed via [3+2] cycloaddition of azide ion with nitrile [14].This procedure suffers from a few drawbacks, e.g. expensive and toxic metal organic azide and nitrile and probability of forming hydrazoic acid which is explosive.There are several catalyst in literature ,e.g. $BF_3.OEt_2$[15], $Pd(OAc)_2/ZnBr_2$[16], $AlCl_3$[17], $Yb(OTf)_3$[18] etc,but there are still a few drawbacks, e.g, tedious separation and recovery of the catalysts.Recently several heterogeneous catalytic system such as nanocrystalline ZnO, Zn/Al HT[19], $FeCl_3/SiO_2$, [20], Cu_2O[21], $CdCl_2$ [22], And metal-modified montmorillonites and zeolite were extensively reported[23]. Many metals, such as Fe, Cu, Mo, V, Zn, Al, Mn, Co were used to improve the effectiveness of montmorillonites[24-31]. These methods also have some drawbacks, such as , these require excess amount of sodium azide, long reaction time, in spite of that , the cycloaddition is too

slow to be practically useful except strong electron withdrawing groups activate the nitrile group. Due to the wide applications of the tetrazole-embedded structures, easy and economical synthetic protocols are still worth exploring[32]. One-pot protocols are particularly important as they get off the isolation of intermediate products[33].One-pot protocols for the synthesis of tetrazole have already been reported in literature using ammonia and iodine[34]. But this methodology should be avoided because this could result in the formation of hydrazoic acid and triiodide monoamine, which are explosive [35]. In view of the availability, lower toxicity and ease of handling of aldehydes as compared to nitriles, the application of aldehydes for the synthesis of tetrazole derivatives are highly attractive and advantageous strategy. Direct transformation of aldehydes to the corresponding tetrazoles via [3+2] cycloaddition is well documented in literature[36-38].Titanium, a very abundant, inexpensive and nontoxic element, has been rarely utilized in organic synthesis. Out of several titanium compounds, a few of them ($TiCl_4$, $TiCl_3$, $TiCl_2(OR)_2$, Cp_2TiCl_2, etc.) are widely used [39]. To the best of our knowledge, $TiCl_3$ has been not yet used for the synthesis of 5-substituted-1H-tetrazole.

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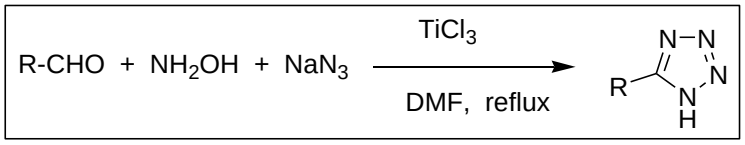
III.B.2. Result and discussion

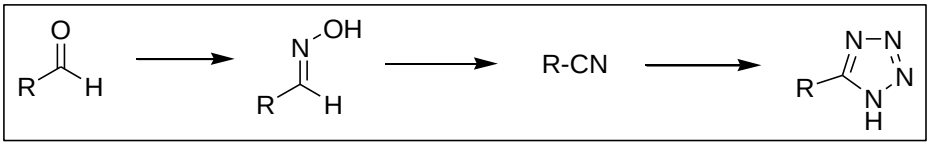
In this connection, herein, we report the protocol, where we used less expensive and easily available starting material aldehydes along with hydroxylamine hydrochloride and sodium azide catalysed by Titanium trichloride resulting in the formation of a number of tetrazole derivatives (1-16) from moderate to excellent yield (**Table. III.B. 1.**). Water solubility of catalyst, non-toxicity, easy work-up, low duration and excellent yield of the products are special feature of this methodology.

The synthesis of tetrazoles (1-16) was achieved by the addition of hydroxylamine hydrochloride, sodium azide, Titanium tri chloride in DMF to various aldehydes and heating at reflux condition to afford the corresponding tetrazoles **(Scheme. III.B. 1.)** after work-up under acidic condition**.** The effect of temperature (Table1), solvent (Table 2) and amount of catalyst (Table3) were monitored. It

was found that DMF was the best solvent (**entry 4, Table. III.B. 2**.). We also optimized the amount of catalyst and it was found to be 20mol% (**entry 4, Table. III.B. 3**.). For the generalization of the reaction, we applied optimized condition i.e. Hydroxylamine hydrochloride (1.2mmol), sodium azide (1.5mmol) and $TiCl_3$ catalyst (20 mol%) under reflux condition to different aldehyde (1mmol) and got 42-95% yield at 3.5-6h (**Table. III.B. 4**.). This strategy applies to all types of aldehydes (aliphatic, aromatic and heterocyclic). The best result was found for aldehydes having electron withdrawing groups.The direct transformation of aldehydes into nitriles is well documented in literature with different reaction conditions [40-42]. Spectroscopic data confirmed the formation of the expected products. The intermediate nitrile is formed first (**Scheme. III.B. 2.**) and then [3+2] cycloaddition reaction takes place between nitrile and azide ion. $TiCl_3$ facilitate the cycloaddition reaction because in absence of $TiCl_3$, only oxime is formed (**Table. III.B. 3., entry 6**).completion of reaction was tested by TLC and after acidic work-up, the desired products were achieved by column chromatography using pet ether and ethyl acetate mixture as eluent.



Scheme. III.B.1. $TiCl_3$ catalyzed one-pot protocol for the conversion of aldehydes into 5-substituted 1H- tetrazole



Scheme. III.B. 2. Proposed reaction intermediate for the synthesis of 5-substituted 1H-tetrazole

Table. III.B. 1: Effect of temperature on the synthesis of 5-substituted 1H-tetrazole[a]

Entry	**Temperature(^{0}C)**	**Yield(%)[b]**
1	Room temp	Nil
2	60	25
3	100	62
4	130	95
5	**reflux**	**95[c]**

[a]Reaction condition: benzaldehyde (1mmol), hydroxylamine hydrochloride (1.2 mmol), sodium azide (1.5mmol), DMF (5ml), $TiCl_3$ catalyst (20mol%) at reflux condition for 4h

[b]Isolated Yield

[c]Optimized condition

Table. III.B. 2: Effect of solvent on the synthesis of 5-substituted 1H-tetrazole[a]

Entry	**Solvent**	**Yield(%)[b]**
1	None	Nil
2	DMSO	60
3	H_2O	20
4	**DMF**	**95[c]**
5	Acetonitrile	30
6	Toluene	Nil
7	THF	Nil

[a]Reaction condition: benzaldehyde (1mmol), Hydroxylamine hydrochloride (1.2mmol), sodium azide(1.5mmol), DMF(5ml), $TiCl_3$ catalyst (20mol%) at reflux condition for 4h

[b]Isolated yield of product

[c]Optimized condition

Table. III.B. 3: Effect of catalyst loading for the synthesis of 5-substituted 1H-tetrazole[a]

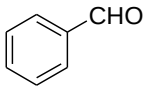
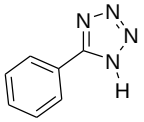
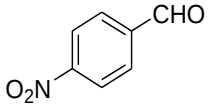
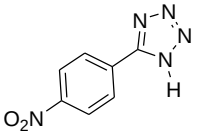
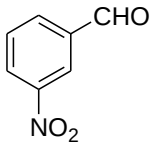
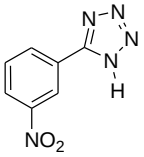
Entry	Catalyst(mol%)	Yield(%)[b]
1	5	40
2	10	67
3	15	95
4	**20**	**95[c]**
5	30	96
6	none	Oxime

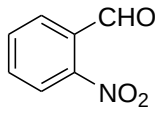
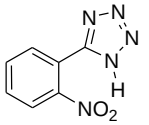
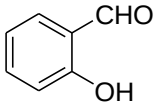
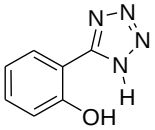
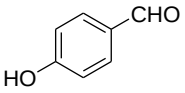
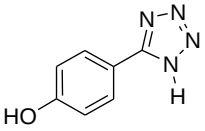
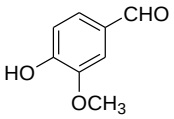
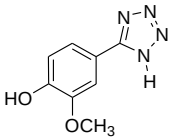
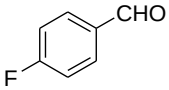
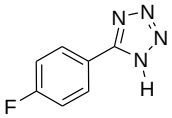
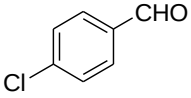
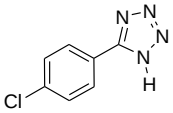
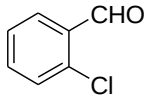
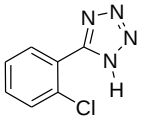
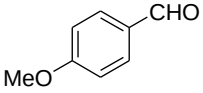
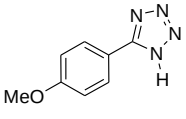
[a]Reaction condition: benzaldehyde (1mmol), Hydroxylamine hydrochloride (1.2mmol), sodium azide (1.5mmol), DMF (5ml), $TiCl_3$ catalyst at reflux condition for 4h

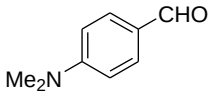
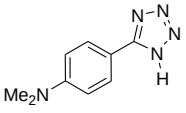
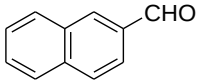
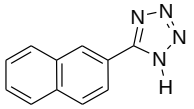
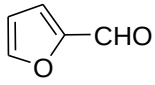
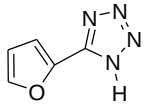
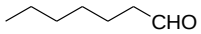
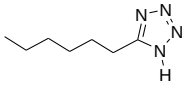
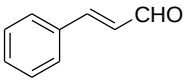
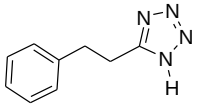
[b]Isolated Yield of Product

[c]Optimized condition

Table. III.B. 4: Synthesis of 5-substituted 1H-tetrazole derivatives[a]

Entry	Reactant	Time(h)	Product	Yield(%)[b]
1		4		86
2		3.5		84
3		3		95

4		4		61
5		5		74
6		4		76
7		5		71
8		3.5		92
9		3		89
10		5		52
11		5		75

12		5.5		82
13		3.5		85
14		3		79
15		6		42
16		4		81

[a]Aldehyde (1mmol), hydroxylamine hydrochloride (1.2 mmol), sodium azide (1.5 mmol) and Titanium trichloride (20mol%) in DMF(5ml) under reflux condition.

[b]Isolated yield

III.B.3. Experimental

III.B.3.1. Chemicals

All the chemicals used for the present investigation are mentioned in **table .III.B.5.**

The source of the chemicals and their purity are listed in **table. III.B.5.**

Table. III.B.5.

Chemicals required for present investigation

Entry	Chemical	Source	Purity(%)
1	Benzaldehyde	Sigma-Aldrich	98
2	4-Nitrobenzaldehyde	LOBA Chemie	98
3	3-Nitrobenzaldehyde	LOBA Chemie	98
4	2-Nitrobenzaldehyde	LOBA Chemie	98
5	2-hydroxybenzaldehyde	S.D. Fine	99
6	4-Hydroxybenzaldehyde	S.D. Fine	98
7	3-Methoxy-4-hydroxy benzaldehyde	S.D Fine	99
8	4-Fluoro benzaldehyde	Fisher Scientific	98
9	4-Chlorobenzaldehyde	S.D.Fine	98
10	2-Chlorobenzaldehyde	S.D.Fine	97
11	4-Methoxybenzaldehyde	S.D.Fine	98
12	N, N-dimethyl-4-aminobenzaldehyde	Sigma-Aldrich	99
13	2-Napthaldehyde	Sigma-Aldrich	98
14	Furfural	Sigma-Aldrich	99
15	Heptaldehyde	Spectrochem	97
16	Cinnamaldehyde	Sigma-Aldrich	98
17	Hydroxylamine hydrochloride	Fisher Scientific	96
18	Sodium azide	LOBA Chemie	99
19	Titanium trichloride	LOBA Chemie	15% solution
20	DMF	Merk	99
21	Sodium sulphate anhydrous	SRL	99.5
22	Petrolium ether	T.B	98
23	Ethylacetate	T.B	99
24	Silica-gel 60-120 mesh for column	SRL	-
25	Silica gel for TLC	SRL	-
26	Potassium bromide for IR	Merk	99
27	DMSO-d_6 for NMR	ACROS	99.8

28	$CDCl_3$ for NMR	ACROS	99.8

III.B.3.2. Reaction procedure and purification

Aldehyde (1mmol), hydroxylamine hydrochloride (1.2mmol), sodium azide (1.5mmol) and titanium trichloride (20 mol%) were added to 5ml DMF and the mixture was kept on reflux for requisite time (Table 4). The progress of reaction was monitored by TLC and after completion of reaction, the mixture was treated with HCl (5ml dil.HCl), thereafter the mixture was added to 100ml water and extracted with ethylacetate, washed by water a few times. The extract was dried over anhydrous Na_2SO_4, purified by column chromatography on silica-gel (60-120 mesh) by pet-ether and ethyl acetate (75:25) as eluent.

III.B.3.3. Spectroscopic measurements

All melting points were determined by open capillary method. IR spectra were recorded on KBr disks on Shimadzu 8300 spectrometer. ^1H and ^{13}C NMR were recorded on 300 MHz Bruker Avance FT NMR spectrometer using TMS as internal standard.

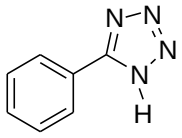
III.B.4. Conclusion

In conclusion, we have explored a lewis-acid, titanium trichloride catalyzed one-pot facile synthesis of 5-substituted 1H-tetrazole from easily available aldehyde (aromatic, aliphatic, heterocyclic), hydroxylamine hydrochloride and sodium azide under reflux condition. Advantages of this methodology are, no use of harmful organic solvent and toxic catalyst, which causes environmental pollution, easy work-up process and excellent yield of products.

III.B.5. Characterization data

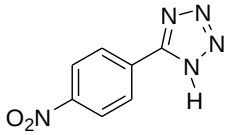
Spectroscopic data of 5-substituted 1H-tetrazole derivatives

1. 5-phenyl-1H-tetrazole



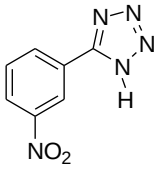
White solid; M.P: 211 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.59–7.65 (m, 3H), 8.04–8.08 (m, 2H).[1] ^{13}C NMR (75 MHz, DMSO-d_6): δ= 126.92, 127.40, 128.15, 129.38, 131.19, 134.23, 155.14

2. 5-(4-nitrophenyl)-1H-tetrazole



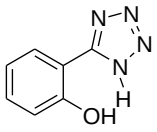
Yellow solid; M.P: 215 ^{o}C. ^{1}H NMR (400MHz, DMSO-d_6): δ = 8.46 (d, J = 8.84 Hz, 2H), 8.32 (d, J = 8.92 Hz, 2H); ^{13}C NMR (75MHz, DMSO-d_6): δ = 123.74, 124.82, 128.43, 129.28, 148.94, 156.02 (C=N), 162.76

3. 5-(3-nitrophenyl)-1H-tetrazole



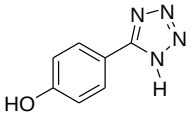
Yellow solid, M.P: 107 ^{o}C. ^{1}H NMR (400MHz, DMSO-d_6): δ = 8.85 (s, 1H), 8.43–8.50 (m, 2H), 7.90–7.94 (m, 1H).[1] ^{13}C NMR (75MHz, DMSO-d_6): δ = 125.05, 129.14, 129.76, 134.79, 136.59, 151.82, 158.64.

4. 2-(1H-tetrazol-5-yl) phenol



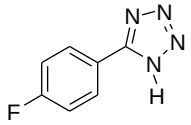
White solid powder; M.P: 217 ^{o}C. ^{1}H NMR (300MHz, DMSO-d_6): δ =7.18 (q, J = 10.2, 2H), 7.54 (s, 1H), 8.14 (d, J = 7.2, 1H). ^{13}C NMR (75MHz, DMSO-d_6): δ = 110.94, 116.81, 120.16, 129.50, 133.08, 152.10, 155.76.

5. 4-(1H-tetrazol-5-yl) phenol



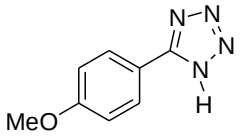
Yellow solid; M.P: 230 ^{o}C. ^{1}H NMR (300MHz, DMSO-d_6): δ = 6.95 (d, J = 6.8, 2H), 7.62 (d, J = 7.8, 2H). ^{13}C NMR (75MHz, DMSO-d_6): δ =115.16, 116.61, 129.22, 130.82, 155.45 (C=N), 160.55.

6. 5-(4-fluorophenyl)-1H-tetrazole



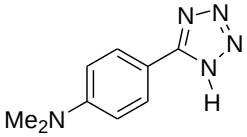
Yellow solid; M.P: 185 ^{o}C.^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.90-8.02 (m, 2H), 7.15-7.33 (m, 2H). ^{13}C NMR (75MHz, DMSO-d_6): δ = 116.64, 121.22, 130.47, 155.14, 165.68

7. 5-(4-methoxyphenyl)-1H-tetrazole



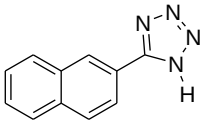
Yellow solid; M.P: 225 ^{o}C. ^{1}H NMR (400MHz, DMSO-d_6): δ = 3.85 (s, 3H), 7.97–8.01 (m, 2H), 7.16–7.19 (m, 2H).[1] ^{13}C NMR (75MHz, DMSO-d_6): δ = 55.70, 113.84, 114.79, 126.76, 128.48, 129.82, 162.11, 162.95.

8. 5-(N, N-dimethyl-4-phenyl)-1H-tetrazole



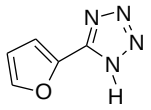
Brownish solid, ^{1}H NMR (300MHz, DMSO-d_6): δ = 3.03 (s, 6H), 6.81 (d, J = 8.4, 2H), 7.83 (m, 2H). ^{13}C NMR (75MHz, DMSO-d_6): δ = 111.14, 121.22, 128.48, 152.36, 155.42.

9. 15-(naphthalene-3-yl)-1H-tetrazole



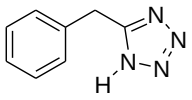
Yellow solid; M.P: 209 ^{o}C ^{1}H NMR (300MHz, DMSO-d_6): δ = 7.65 (d, 2H), 8.03-8.26 (m, 2H), 8.67 (s, 1H); ^{13}C NMR (75MHz, DMSO-d_6): δ = 122.19, 124.27, 127.81, 128.44, 129.22, 129.76, 133.25, 134.48, 155.14

10. 5-(furan-2-yl)-1H-tetrazole



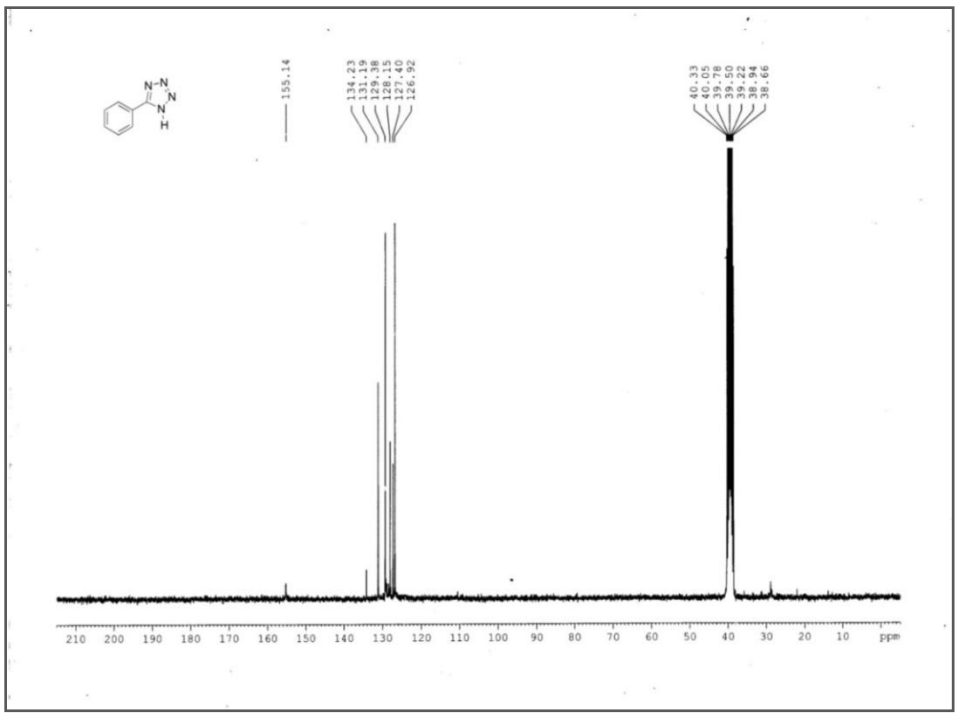
Yellow solid; M.P: 201 ^{o}C. ^{1}H NMR (300MHz, DMSO-d_6): δ = 6.33-7.10 (m, 1H), 7.20-7.34 (m, 1H), 7.52-8.07 (m, 1H); ^{13}C NMR (75MHz, DMSO-d_6): δ = 112.86, 113.42, 140.30, 146.40, 148.70

11. 5-benzyl-1H-tetrazole

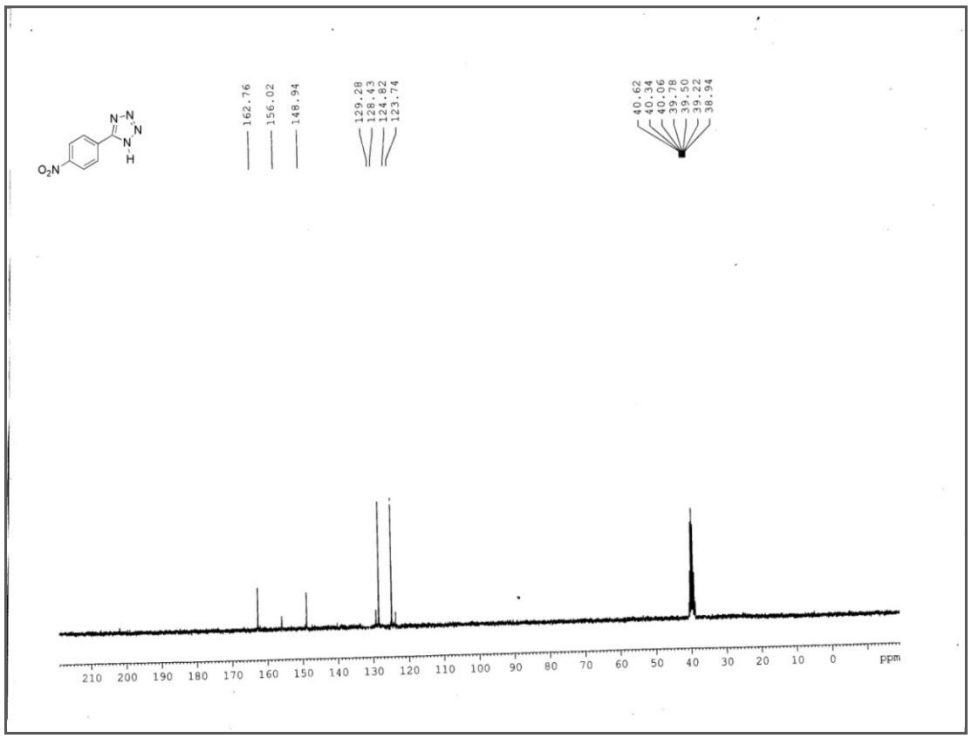


White solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.34 (s, 2H), 7.33-7.38. ^{13}C NMR (75MHz, DMSO-d_6): δ = 29.33, 127.47, 129.11, 129.18, 155.68.

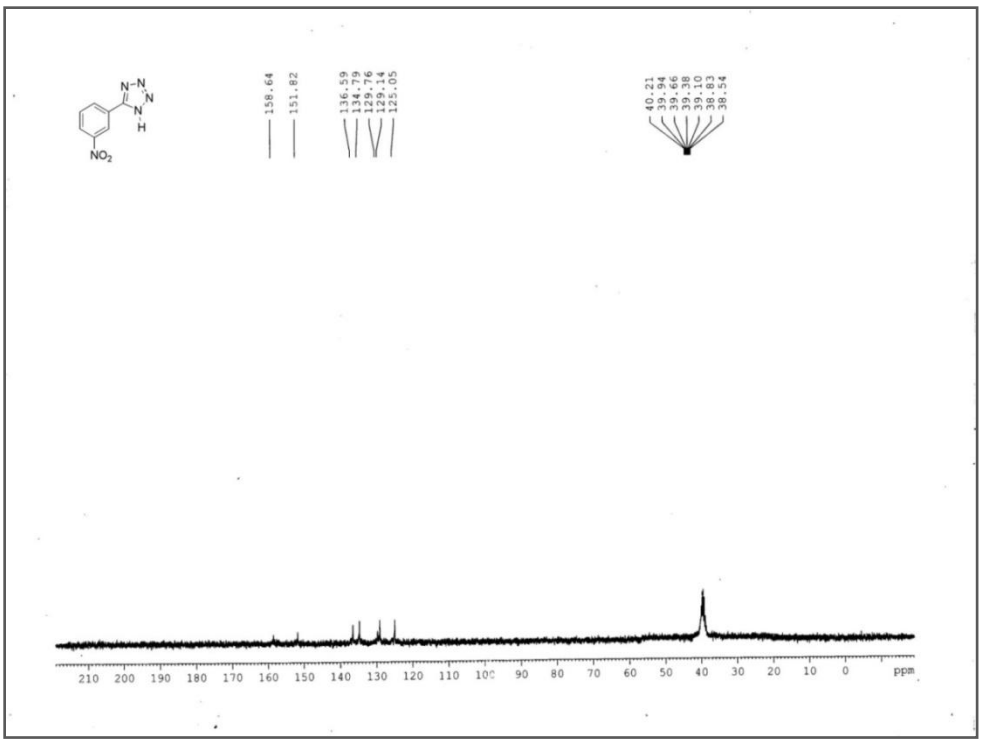
III .B.6. Supporting Spectra



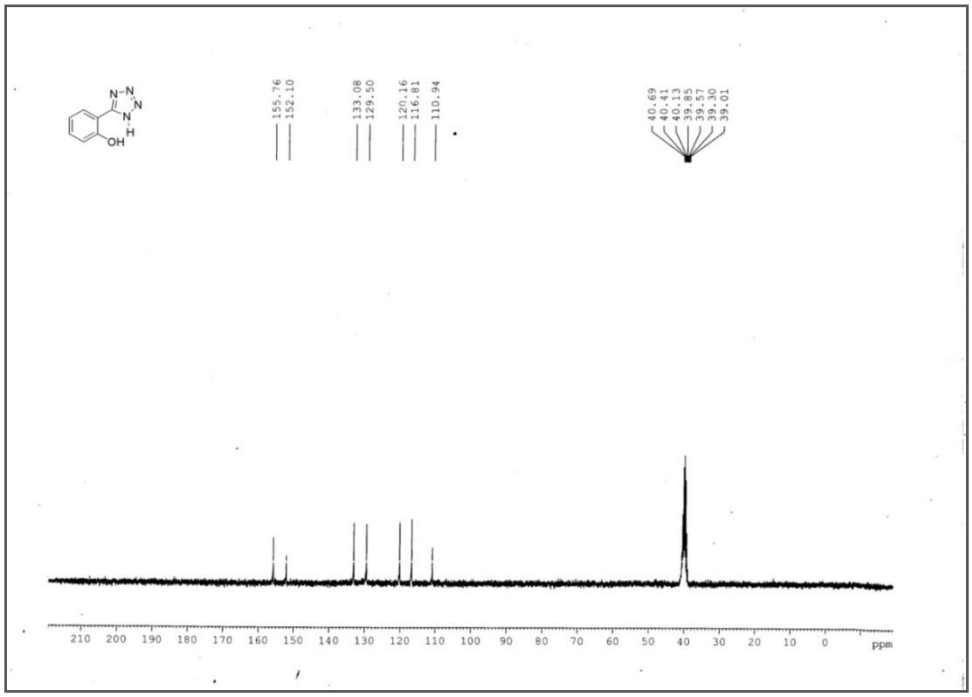
III.B.6.1. ^{13}C NMR spectrum of 5-phenyl-1H-tetrazole



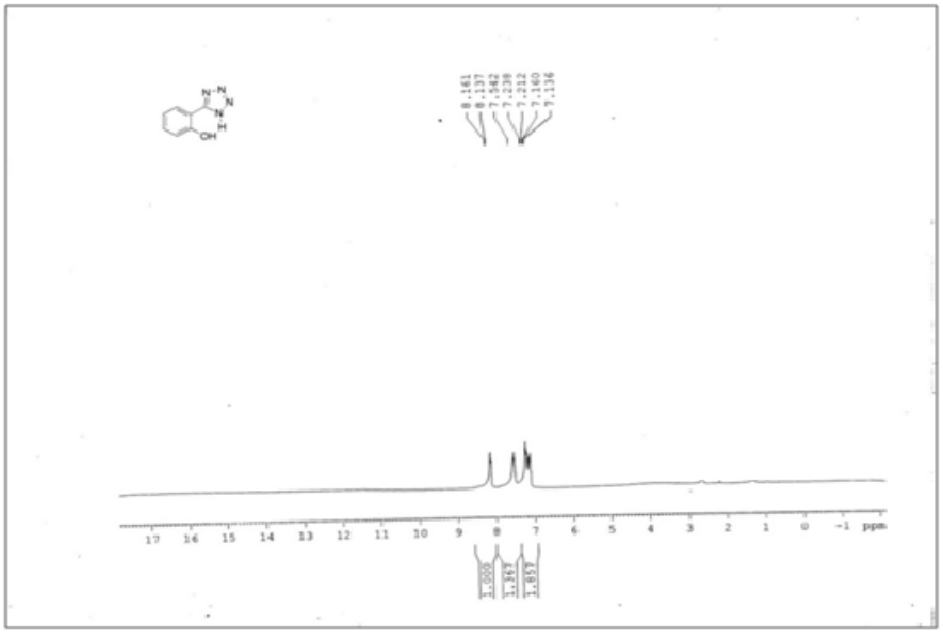
III.B.6.2. ^{13}C NMR spectrum of 5-(4-nitrophenyl)-1H-tetrazole



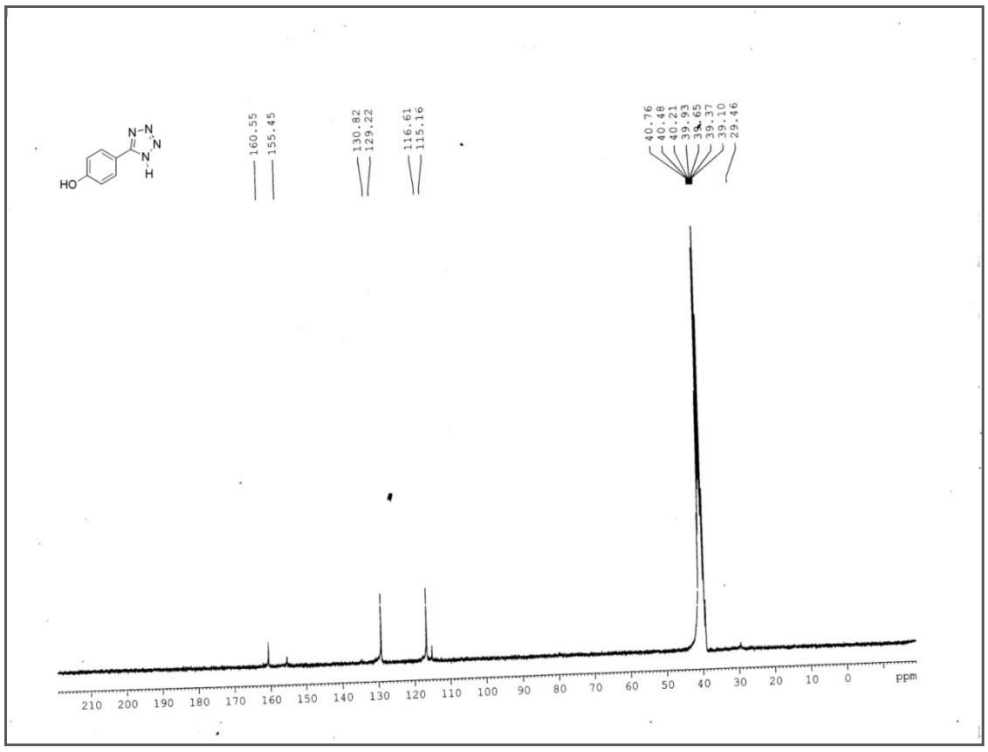
III.B.6.3. ^{13}C NMR spectrum of 5-(3-nitrophenyl)-1H-tetrazole



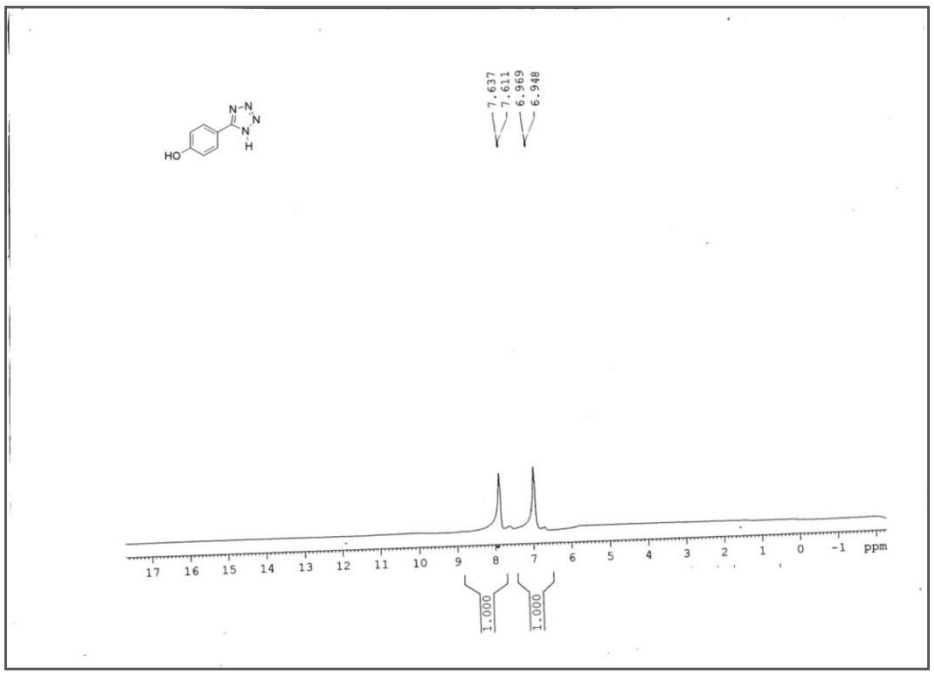
III.B.6.4. ^{13}C NMR spectrum of 2-(1H-tetrazol-5-yl) phenol



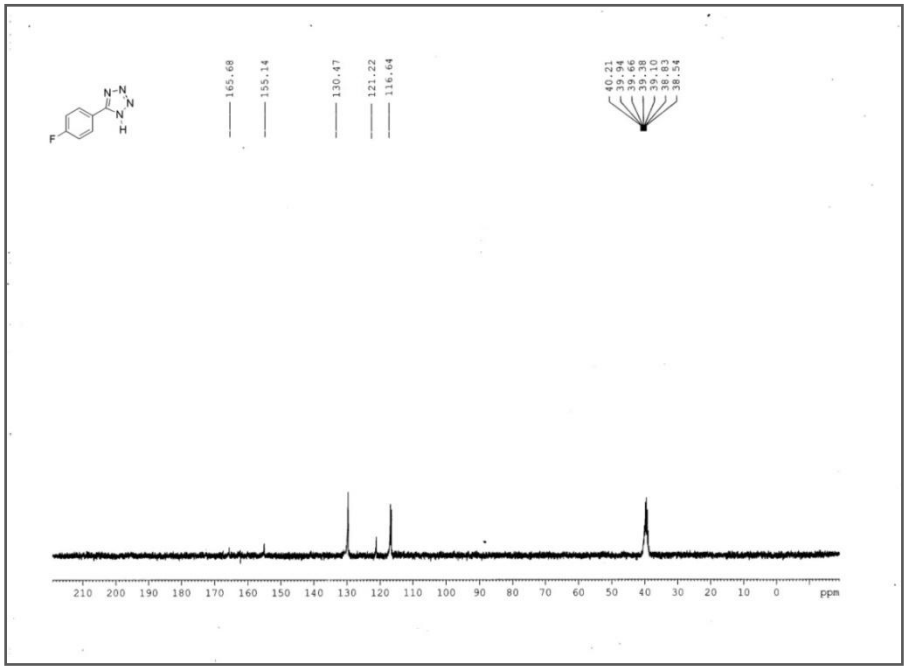
III.B.6.5. ^{1}H NMR spectrum of 2-(1H-tetrazol-5-yl) phenol



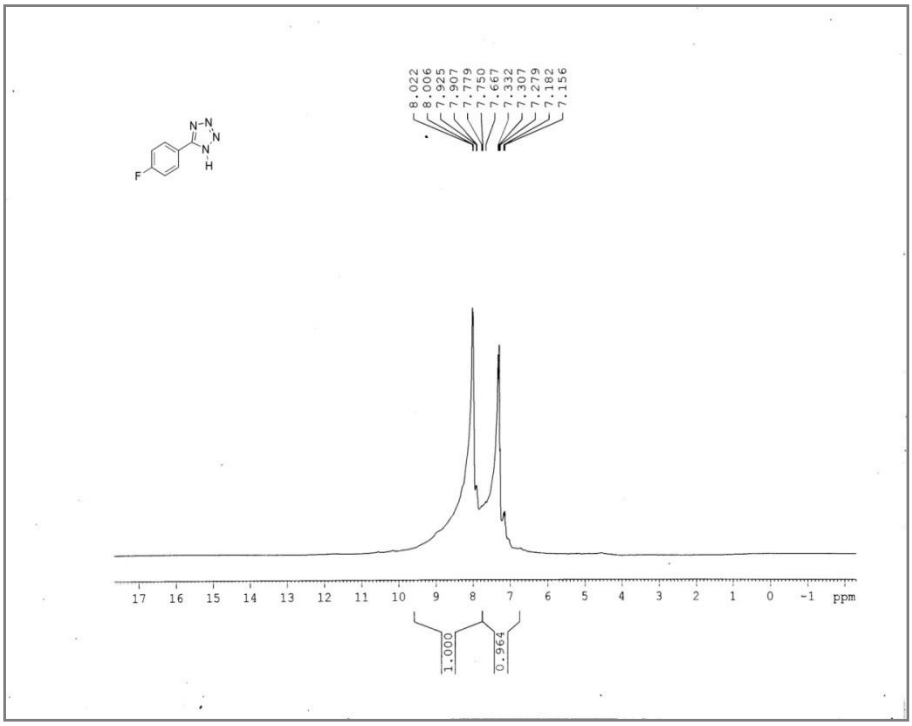
III.B.6.6. ^{13}C NMR spectrum of 4-(1H-tetrazol-5-yl) phenol



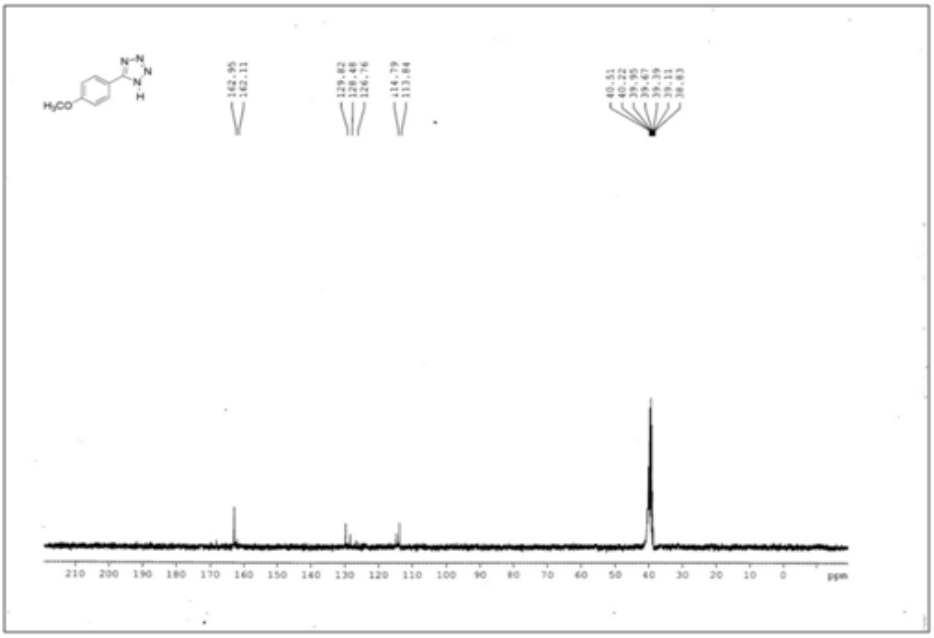
III.B.6.7. . ^{1}H NMR spectrum of 4-(1H-tetrazol-5-yl) phenol



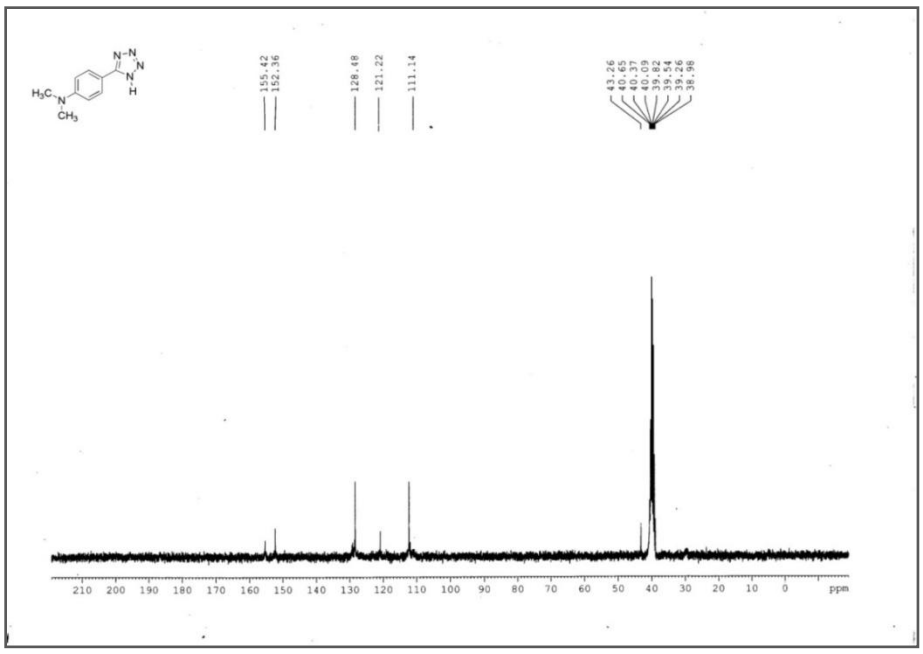
III.B.6.8. ^{13}C NMR spectrum of 5-(4-fluorophenyl)-1H-tetrazole



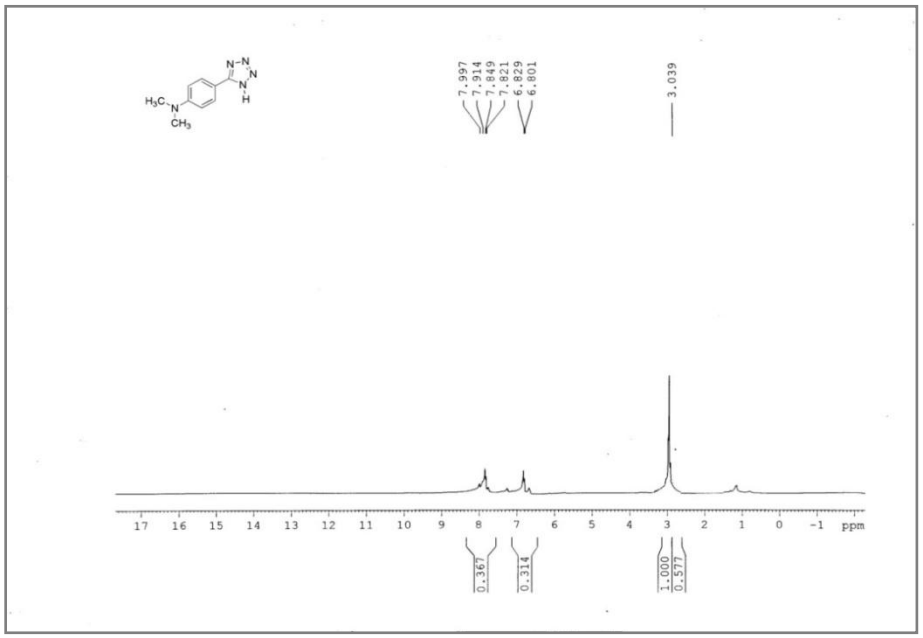
III.B.6.9. ^{1}H NMR spectrum of 5-(4-fluorophenyl)-1H-tetrazole



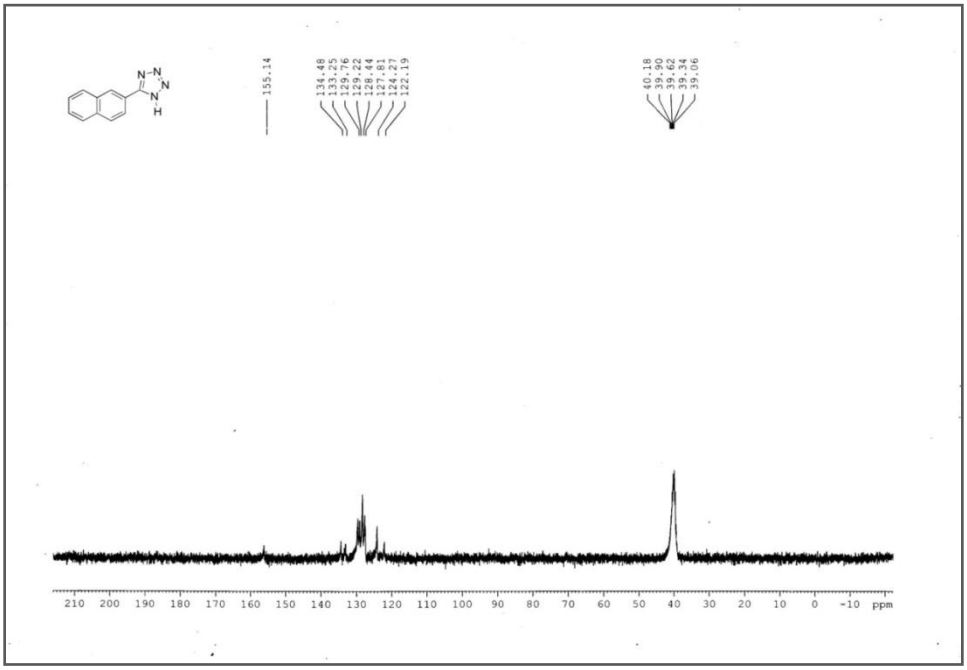
III.B.6.10. ^{13}C NMR spectrum of 5-(4-methoxyphenyl)-1H-tetrazole



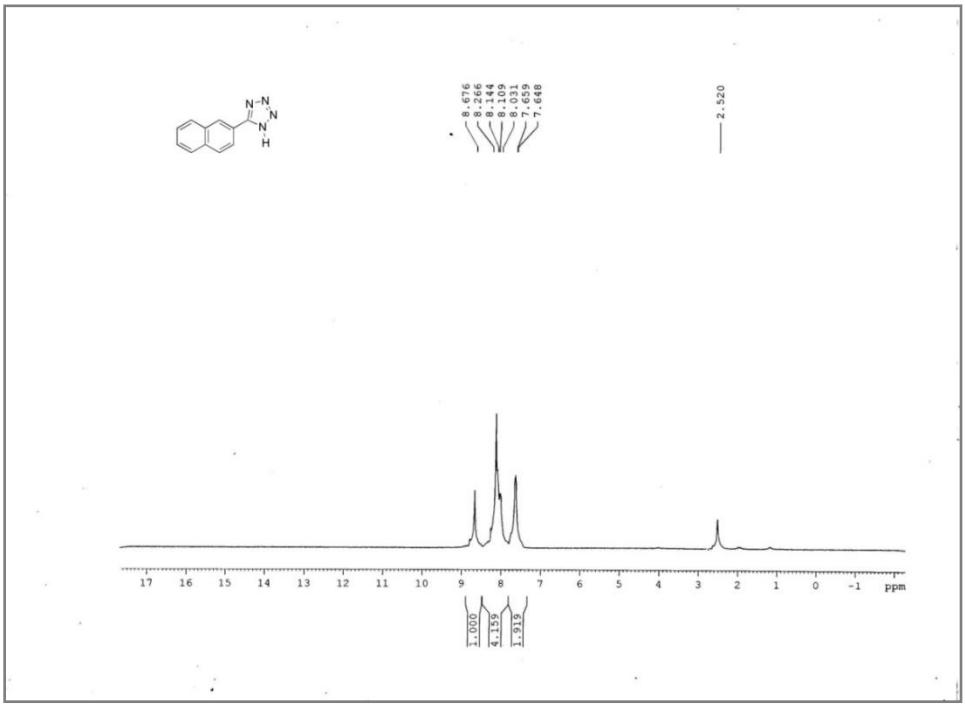
III.B.6.11. ^{13}C NMR spectrum of 5-(N, N-dimethyl-4-phenyl)-1H-tetrazole



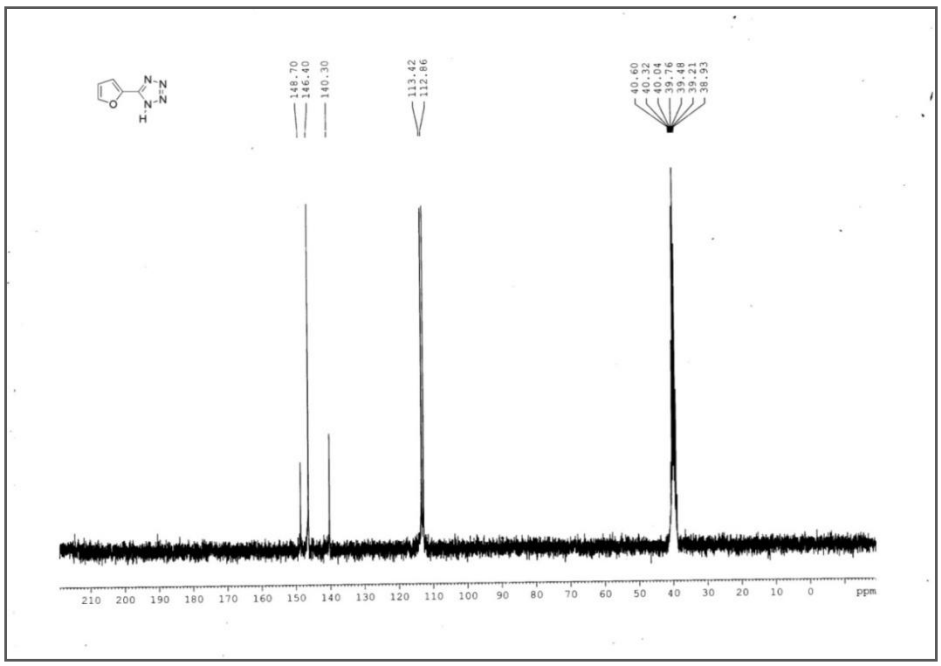
III.B.6.12. ^{1}H NMR spectrum of 5-(N, N-dimethyl-4-phenyl)-1H-tetrazole



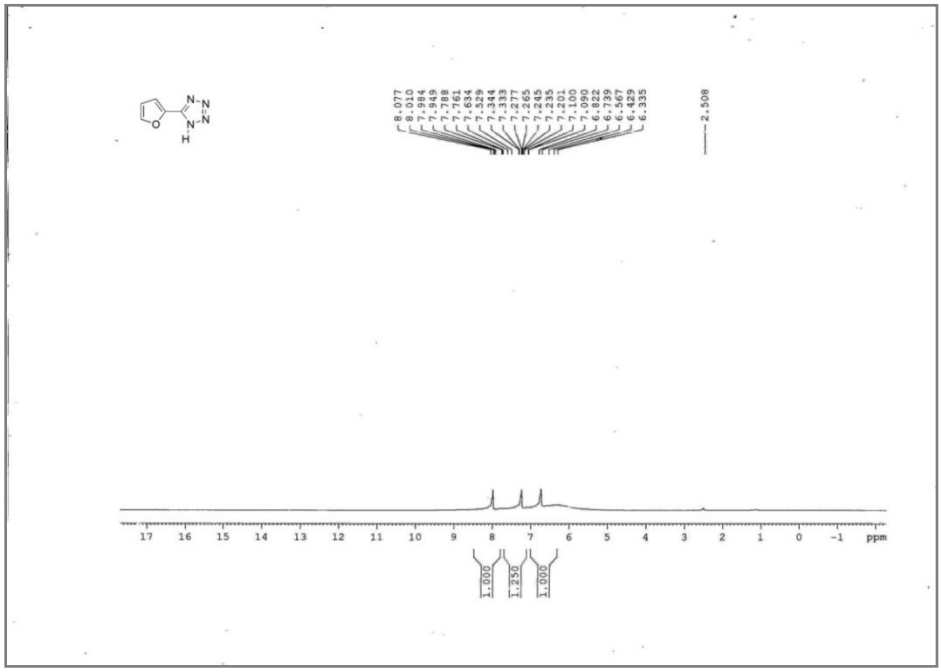
III.B.6.13. . ^{13}C NMR spectrum of 15-(naphthalene-3-yl)-1H-tetrazole



III.B.6.14. ^{1}H NMR spectrum of 15-(naphthalene-3-yl)-1H-tetrazole



III.B.6.15. ^{13}C NMR spectrum of 5-(furan-2-yl)-1H-tetrazole



III.B.6.16. ^{1}H NMR spectrum of 5-(furan-2-yl)-1H-tetrazole

III.B.7. References

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Letters in Organic Chemistry, 2017, *14*, 566-570

RESEARCH ARTICLE

Clean and Green Approach for One-pot Synthesis of Pyrazines from Ethylenediamine and 1, 2-Diketone or Its Analogues Under Neat Reaction Condition

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ARTICLE HISTORY

Received: November 25, 2016
Revised: April 03, 2017
Accepted: May 15, 2017

DOI:
10.2174/1570178614666170609072519

Abstract: ***Background***: Compounds having N-heterocyclic moieties are of huge importance in the field of agrochemical, pharmaceutical, biological, fragrances, *etc.* Due to a lot of applications associated with pyrazine moieties, their synthesis has always been important for organic chemists.

Method: Surfeit synthetic methodologies are documented in literature. Most of the methodologies used expensive solvents, harmful metal catalyst and all suffer from rigorous work-up procedures. An efficient, environmentally benign methodology, needs to be developed. We mixed ethylenediamine (2mmol) with 1,2-diketone(1mmol), later, α-hydroxy ketone and α-bromo ketone on magnetic stirrer at room temperature under neat reaction condition for 5 to 10 hrs.

Results: After purification by column chromatography using silica gel(60-120 mesh) and pet-ether, ethylacetate mixture as eluent, we achieved pyrazine derivatives from moderate to high yield.

Conclusion: Efficient and clean procedure for one-pot preparation of pyrazines from ethylenediamine and 1,2-diketones or with α-hydroxy ketone or with α-bromo ketone has been carried out under neat reaction condition at room temperature. Environmentally benign process furnishing moderate to excellent yields of the product and simple work-up giving pure products are special features of this reaction.

Keywords: 1,2-Diketone, ethylenediamine, environmentally benign process, pyrazine, moieties, column chromatography.

1. INTRODUCTION

Heterocyclic compounds are omnipresent in nature [1]. Among different N-heterocyclic compounds, pyrazine and its congeners have broad spectrum of biological activities [2] such as anticancer, antituberculosis [3], antimicobacterial activity, antimalarial, antiHIV and cytotoxicity [4]. In addition, these heterocycles are widely applied to other industrial fields, for example, in the preparation of perfumes, pharmaceuticals, agricultural chemicals [5]. It also plays an important role in making flavor ingredient in food and pheromones in various insects [6, 7]. It is a versatile synthetic intermediates [8]. Owing to vast and outstanding applications, several synthetic strategies have been developed for their synthesis over the years [9]. Among several methods developed, pyrazines are formed by catalytic dehydrogenation of the vapour of ethanolamine. The catalysts used were copper oxide, zinc oxide, copper, sodium carbonate [10]. Condensation of α-amino ketone [11], Pd-catalyzed cross coupling reaction also produced pyrazine derivatives [12]. Further, pyrazine compounds were prepared by the reaction of diamine with diol in vapour phase, catalyzed by granular alumina [13]. Catalytic systems such as copper-zinc-chromium [14], zinc-phosphoric acid-manganese [15], copper-chromium [16] and silver [17] were also used for the preparation of 2-methyl pyrazine from propyleneglycol and ethylenediamine. Pyrazines were synthesized from the condensation of epoxides and diamines using copper-chromium catalyst [18]. Piperazines gets dehydrogenated in the presence of palladium catalyst to produce pyrazines in high yield [19]. α-Hydroxy ketones and 1,2-diamine also to produce pyrazines *via* MnO_2 catalyzed tandem oxidation reaction under refluxing conditions, but the yields were not so encouraging [20], moreover this reaction requires an excess amount of MnO_2 catalyst that detracts from the commercial point of view and green condition [21]. Direct condensation of 1,2-diketones with 1,2-diamine has so far been the better procedure of pyrazine synthesis through dihydropyrazine [22]. Although, there are several methods of pyrazine synthesis in literature, most of them are regarded as ineffective because of poor yield, long reaction time, tedious work-up process and drastic reaction condition [23]. Although, few of them are apparently successful, but conven-

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1875-6255/17 $58.00+.00

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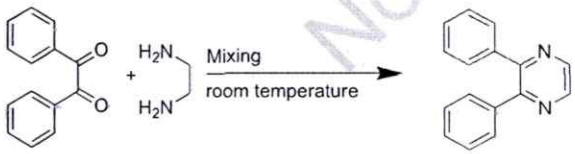
ient and milder laboratory procedures for dehydrogenation were unsuccessful and most of the methods are limited by long reaction time, use and generation of hazardous substances and heavy metals as the catalyst [24]. Therefore the development of efficient, mild and environmental friendly method for pyrazine synthesis has been a long cherished goal for organic chemists.

Recently, environmentally-friendly reaction processes have been extensively studied from the view point of green chemistry. Solid acid catalyst under heterogeneous condition [25] plays an important role in organic synthesis. Generally solid acid catalysts are clay and silica based [26]. But these types of reaction require an appreciable amount of solvent in work-up process [27]. The concept of neat reaction is consistent with the dream of green chemistry in true sense. Neat reaction is a solvent-free methodology where a mixture of reactants is grinded in the absence of any solvent. The easy work-up and devoid of any solvent makes it justified from the stand point of green chemistry.

The primary demands of green synthesis include minimization of steps, that is one-pot tandem reactions as well as catalytic processes under metal-free conditions [28]. Since there is no method developed for the one-pot and metal-free tandem synthesis of pyrazines from ethylenediamine with 1,2-dicarbonyl compounds or analogues, we were interested to develop an alternative solvent and metal-free greener process for the synthesis of pyrazines directly from ethylenediamine with 1,2-dicarbonyl compounds or with analogues at room temperature. In recent days, solvent-free syntheses have attracted the attention of chemists because they are environmentally benign processes. In continuation of our interest in the development of solvent-free synthesis [29], herein we report a new synthetic strategy for the preparation of pyrazine derivatives from ethylenediamine with 1,2-diketone or with analogues under neat reaction condition.

In connection with our present interest, we explored the synthesis of pyrazines through the metal-free, solvent-free tandem condensation in one-pot protocol (Scheme **1**).



Scheme (1). One- pot condensation of ethylenediamine with 1,2-diketone or with analogues resulting pyrazines derivatives.

2. MATERIALS AND METHOD

All the melting points were determined in an open capillary method. UV spectra were recorded in JASCO V-530 UV/VIS Spectrophotomete, IR was recorded in perkin-Elmer FT-IR Spectrophotometer; NMR was recorded in Bruker Advance 300 MHz FT-NMR instrument using TMS as the internal standard. NMR spetra were recorded in $CDCl_3$. The chemicals used were purchased from Merck, Thomas-Baker and were used as received. No further purification was done.

2.1. Preparation of Pyrazine Derivative

1 mmol of recrystallised benzil and 2mmol of ethylenediamine were added to a mortar. The mixture was grinded for a few minutes and transferred to a 50 ml round bottom flask and was kept stirring with a magnetic spinning bar for 6 hrs. The reaction was checked by TLC (ethylacetate and pet-ether). The product was extracted by ethylacetate, washed by water and filtered through Na_2SO_4. Product was purified by column chromatography using Silica-gel. Petroleum ether-Ethylacetate(PE-EA)mixtures were used as eluent. All the products were characterized by IR, ^1H NMR and ^{13}C NMR.

3. RESULTS AND DISCUSSION

We report herein our findings that finally established a practical and clean procedure for the synthesis of pyrazine derivatives directly from ethylenediamine and 1,2-diketone or with analogues *via* one-pot condensation reaction under metal-free condition at room temperature. There was no other by-product detected by the analysis of the crude product, the conversion was high and the isolation of the desired pyrazine was achieved in excellent yield. A large variation of functional groups attached with the aromatic ring of 1,2-diketones was observed with excellent conversions to pyrazines derivatives (Scheme **1**).

Our studies began with the reaction of ethylenediamine and benzil under neat reaction condition. Initialy we set-up the reaction by adding the reacting components *i.e.* mixture of ethylenediamine(1mmol) and benzil(1mmol) mixture into a glass plate and stirred with a glass rod at room temperature and left for 10 hrs. The reaction mixture was then extracted with ethyl acetate and washed several times by water and the extract was filtered through anhydrous Na_2SO_4. Finally 56% 2,3-diphenyl pyrazine (entry 2, Table **1**) along with unreacted benzil were separated by column chromatography over silica-gel (60-120 mesh) where pet-ether and ethyl acetate mixture was eluent. Thereafter we used mortar for grinding the reaction mixture for a few minutes and transferred the mixture into a 50 ml round-bottom glass bottle and it was kept under magnetic stirrer for better result. We raised the reaction temperature upto 100°C and found no product. We used mono ketone(acetophenone) with ethylenediamine but the reaction was unsuccessful.

Encouraged by the model reaction with benzil and ethylenediamine on neat reaction condition, several experiments regarding time and proportion optimization were carried out for the newly developed general protocol for the synthesis of pyrazine derivatives (Table **1**). Finally we could optimize the reaction condition as benzil(1mmol) and ethylenediamine (2mmol) mixture was kept on magnetic stirrer for 6 hrs and got 2,3-diphenyl pyrazine (77%) as a sole product (entry 3, Table **1**).

In order to show the general applicability, we attempted the recent procedure to a number of chemically diversified ketone and ethylenediamine to synthesize pyrazine derivative (Table **2**, see supporting information file for full experimental data) and obtain the identical result in each case. In the present investigation, it is found that no additional steps required to aromatize the dihydropyrazine derivatives as reported in the early methods and this is the main advantage of this procedure.

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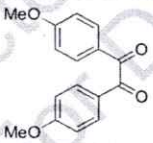
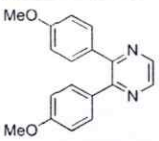
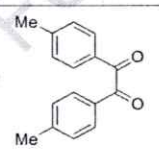
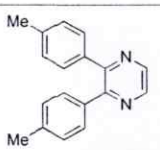
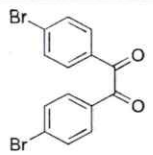
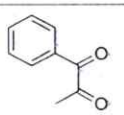
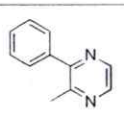
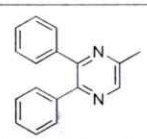
Table 1. Optimization of reaction conditions for one-pot condensation of ethylenediamine(mmol) with benzil(mmol).

Entry	Temp (°C)	Ethylenediamine (mmol)	Benzil (mmol)	Time	Conversion (%)[a]
1	100	1	1.0	12	Nil
2	RT	1	1.0	10	56
3	RT	2	1.0	6	77[b]
4	RT	1/2	1.0	8	42
5	RT	1	1	1	38
6	RT	1	1	2	34
7	RT	1	1	1/2	25

[a]Isolated yield. [b]Optimized reaction condition.

Table 2. Condensation of ethylenediamine with 1,2-dicarbonyl compounds or with α-hydroxy ketones or with α-bromo ketone at room temperature.

Entry No.	Ethylenediamine	1,2-Diketone	Time (h)	Product	Yield (%)
1			6		77
2			6		75
3			6		68
4			10		76
5			8		81
6			7		80
7			6.5		75
8			5		73

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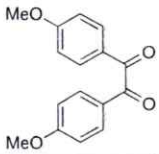
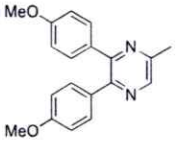
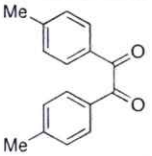
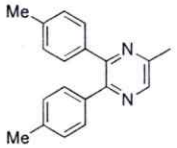
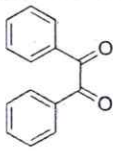
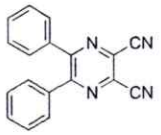
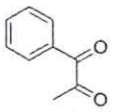
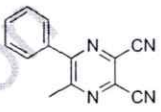
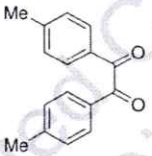
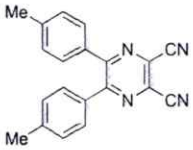
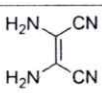
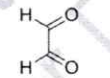
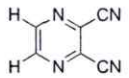
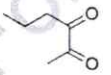
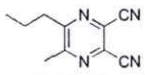
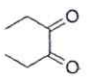
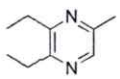
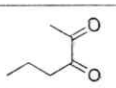
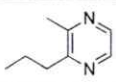
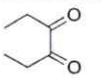
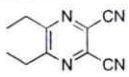
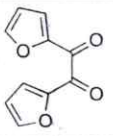
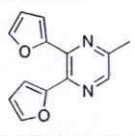
(Table 2) Contd....

Entry No.	Ethylenediamine	1,2-Diketone	Time (h)	Product	Yield (%)
9			5.5		73
10			6		85
11			5		85
12			7		86
13			6		75
14			6.5		82
15			5.5		75
16			7		73
17			8		76
18			7		72
19			5.5		81

Note: % Yield refers to the isolated yield of all compounds.

With the optimized condition (as in Table **1**, entry 3), we examined its practical application with a variety of 1,2-diketone derivatives or with analogues. The results are presented in Table **2**. It can be seen that different keto compounds undergo one-pot condensation with ethylenediamine and gave rise to the formation of corresponding pyrazines in excellent yields.

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In summary, the present work demonstrates the synthesis of bio-active scaffold pyrazine derivatives directly from ethylenediamine and 1,2-diketone or with its analogues *via* one-pot condensation reactions under neat reaction condition at room temperature. The conditions are straightforward, mild, eco-friendly and no other side-products are obtained. Green process for the preparation of pyrazines from ethylenediamine and keto-compounds is developed that could override the existing metal-catalyzed reaction conditions.

CONCLUSION

In conclusion, we have explored a solvent and metal catalyst free, one-pot facile synthesis of pyrazine derivatives from ethylenediamine(2mmol) and 1,2-diketone or with α-bromo and α-hydroxy ketone(1mmol) under neat reaction condition at room temperature. Advantages of this protocol are, avoiding harmful organic solvent which causes environmental pollution, excellent yield and easy work-up process.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Author is thankful to UGC New Delhi for financial support.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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