Sonication Assisted Aza-Michael Addition to Acrylonitrile under Neat and Catalyst Free Conditions

A

Thesis submitted

In partial fulfillment of the requirements for the degree of

M.Sc. (Chemistry)

Submitted by:
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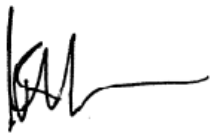
All these thanks are, however, only fraction of what is due to Almighty for granting me an opportunity and strength to successfully accomplish this assignment.

Date: 11.6.09



Ruchika Mishra

Candidate's Declaration

I hereby declare that the work being presented in the thesis entitled **"Sonication assisted Aza Michael Addition to Acrylonitrile under Neat and Catalyst Free Conditions''** in partial fulfillment of the requirements for the award of the degree of Masters in Chemistry and being submitted to Thapar University, Patiala, is my own work during the period of Jan 2009 to May 2009, under the supervision of Dr. Satnam Singh, Assistant Professor, School of Chemistry and Biochemistry, Thapar University, Patiala. I have not submitted the contents embodied in this thesis for the award of any other degree.

Patiala

Date: 11.6.09

Ruchika Mishra

This is to certify that the above statement made by the candidate is correct and true to the best of our knowledge.

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Certificate

This is to certify that thesis entitled **"Sonication Assisted Aza Michael Addition to Acrylonitrile under Neat and catalyst Free Conditions''** being submitted by **Ms. Ruchika Mishra** to Thapar University, Patiala in partial fulfillment of the requirements for the award of degree of M.Sc (Chemistry) is a record of candidate's own work carried out by her under my supervision and guidance and that no part of this thesis has been submitted in part or fully to any other university or institution for the award of any degree.

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Abstract

A Highly efficient method for conjugate addition of different amines on α, β –unsaturated compound (acrylonitrile) was developed in search of new greener method for Michael addition reaction.

A novel method involving solvent free and catalyst free condition for Michael addition reaction has been achieved under sonication. Michael acceptor and different amines were allowed to react under sonication to obtain various Michael adducts in excellent yields which has not been reported till now. This method can be described as the greenest method for Aza-Michael addition in which reaction involves a simple addition of different molecules (Michael acceptor and a nucleophile). There being not a single by-product of the reaction. Moreover, solvent is not used thereby making the reaction economical and safer.

List of Contents

1. Introduction

In the 20th century, chemists envisioned chemistry as the solution to a host of society's needs as stated in DuPont slogan, "Better things for better living through chemistry." However in the 21st century the focus has shifted towards how we do chemistry with regard to the harmful effect of chemicals to our environment.

In the past one decade, there is worldwide demand for ecofriendly chemical synthesis that requires the development of novel and cost effective approaches. One of the most attractive concepts to meet this requirement is 'Green Chemistry' coined by Professor Paul Anastas. Introduced in early 1990's, green chemistry may be defined as the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products. The concept of green chemistry is enshrined in set of 12 principles.

1.1 The 12 guiding principles of Green Chemistry

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all the materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents etc.) should be made unnecessary wherever possible and innocuous when used.
6. Energy requirements for the chemical process should be minimum. Synthetic methods should be conducted at ambient temperature and pressure. Energy can be provided in terms of Ultrasound and Microwave.

7. Raw materials should be obtained from renewable feedstock rather than nonrenewable sources.

8. Unnecessary derivatization (blocking group, protection/deprotection, and temporary modification of physical/chemical processes) should be avoided.

9. Use of catalyst can do wonder in terms of lowering energy requirement and speeding up the reactions.

10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.

11. Analyze in real time to prevent pollution: Include in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.
12. Minimize the potential for accidents: Design chemicals and their forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases to the environment.

The driving force for ultrasound developments in organic synthesis has many facets: It meets the environmental requirement of clean technology as it offers cleaner reactions by improving product yields and selectivity. It also enhances product recovery and purification processes. Sonication allows the use of non-activated and crude reagents as well as an aqueous solvent system; therefore it is friendly and non toxic. It has also improved the traditional reactions which use expensive reagents, strongly acidic conditions, long reaction times, high temperatures, unsatisfactory yields and incompatibility with other functional groups. Therefore, among the new chemistries evolved, Sonochemistry has taken a particular place.

1.2 Sonochemistry

Sonochemistry is a branch of chemical research dealing with the chemical effects and applications of ultrasonic waves i.e. sound with frequencies above 20 KHz that lie beyond the upper limit of human hearing.

1.3 Ultrasound

Ultrasound is the name given to sound waves having frequencies higher than those to which human ear can respond, i.e. greater than 16 KHz and with wavelength between 7.0 and 0.015cm. It is transmitted through any substance -solid, liquid or gas which possesses elastic properties. The ultrasounds can introduce chemical effects seems to be surprising at first glance as its energy is too low to alter electronic, vibrational or rotational molecular states. However a phenomenon called **Acoustic cavitation** is responsible for its chemical effects.

Ultrasound waves are longitudinal and on passing through a liquid media create a series of compression and rarefaction. As the molecules of medium vibrate, the average distance between the molecules decrease in a compression cycle and increase in a rarefaction. When a large negative pressure is applied to a liquid, the intermolecular van der waals forces are strong enough to maintain cohesion, liquid breaks down and small cavities or gas filled microbubbles are formed. The rapid nucleation, growth and collapse of these bubbles constitute the phenomenon of Acoustic cavitation. These bubbles can be filled with gas or vapour and occur in water, organic solvents, biological fluids etc.

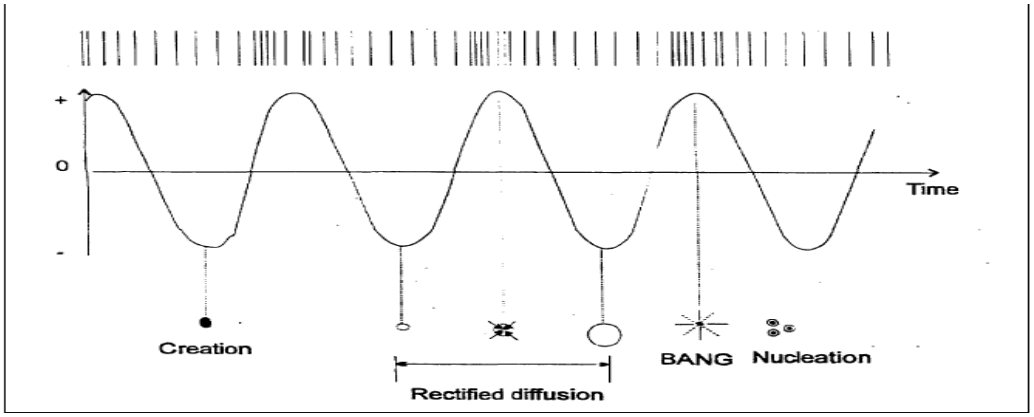
Theoretical sonochemists distinguish between two types of cavitation: stable and transient.

Stable cavitation

These cavitations are formed when microbubbles mainly contain a gas and their mean life is very much longer than an acoustic cycle of ultrasound. They simply oscillate radially with the sound wave and are not responsible for the chemical effects of ultrasound.

Transient cavitations

Their life time is only a few acoustic cycles long during which they expand to 2 to 3 times their initial size. Under proper conditions, these collapse violently during next compression half cycle as shown in following figure.



The local pressures and temperatures generated by this collapse are enormous and chemical effects arise directly from this phenomenon. The collapse of such bubbles release pressure as high as 1000 atm and temperatures 5000K[1]

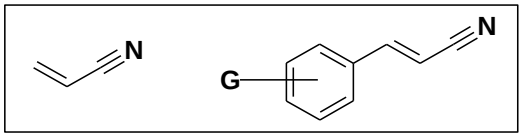
2. Michael Addition Reaction an Overview:

The Michael addition, named for Arthur Michael, is a facile reaction between nucleophiles and activated olefins and alkynes in which the nucleophile adds across a carbon–carbon multiple bond.[2] Addition of a nucleophile (carbon, nitrogen, oxygen and sulfur) to an α, β –unsaturated compound is called as Michael addition reaction.

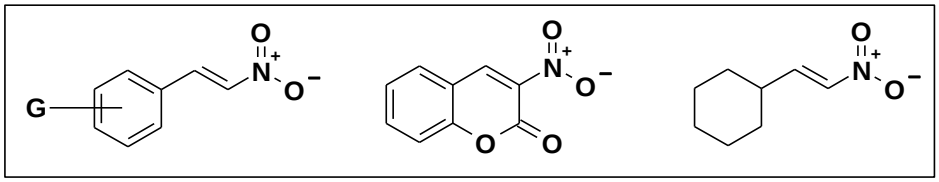
The Michael reaction is one of the most important carbon–carbon or carbon – hetero atom bond-forming reactions. A variety of Michael acceptors, such as α, β -unsaturated ketones, aldehydes, esters, nitriles and nitro compounds can be used in this reaction, which can be readily transformed into a range of different functionalities.[3] A large number of methods have been reported quite recently for 1,4-conjugate addition to electron-deficient olefins. Following are some the types of Michael acceptors:

- **α, β -unsaturated ketones (Chalcones):**

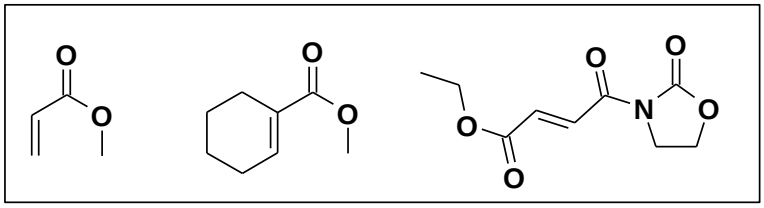
- **α, β –unsaturated nitriles:**



- **α, β –unsaturated nitro compounds:**



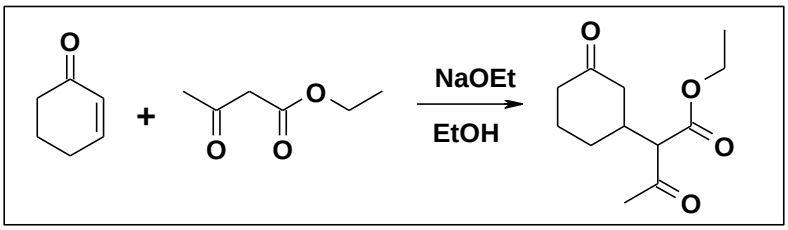
- **α, β –unsaturated esters:**



2.1 Types of Michael Addition Reactions:

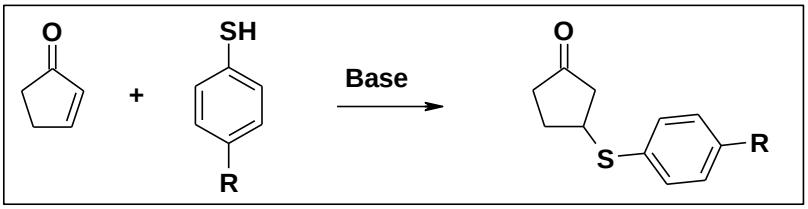
- **Carba-Michael addition:** When an active methylene group present in compounds such as malonic ester, malonitrile, ethylacetoacetate, ethyl cyano acetate etc. generates a carbanion in basic condition to react with any of α, β–unsaturated compound the reaction is known as a carba- Michael addition reaction. Many organometallic compounds too react in the same way.

Example:



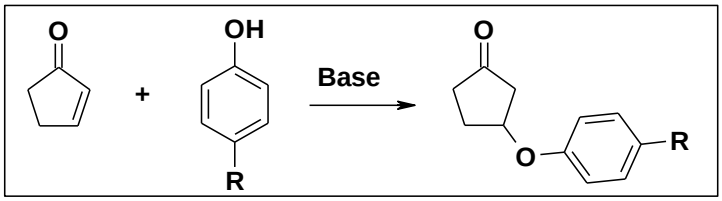
- **Thio-Michael addition:**[4] When a free thiol in basic condition reacts an α β –unsaturated compound the reaction is known as thio-Michael addition reaction. The product obtained in this reaction is β-thio ether as shown :

Example:



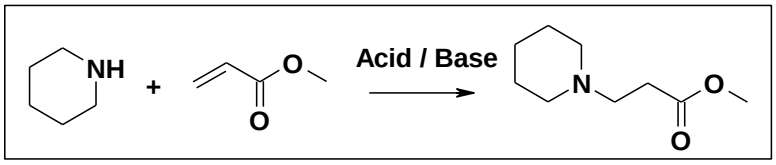
Oxa-Michael addition: When a free alcohol in basic condition reacts with an α, β –unsaturated compound the reaction is known as oxa-Michael addition reaction. The product obtained in this reaction is β-oxo ether.

Example:



- **Aza-Michael addition**: Addition of free amines to α β –unsaturated compound in the presence of acid or base is called as aza Michael addition reaction.

Example:



In general:

All the above reactions are also carried out in Asymmetric manners which are reported in the literature. More recent advances include asymmetric Aza-Michael addition reactions.

2.2 Methods for Michael Addition

Classical method:

The reaction when carried out under ordinary reaction conditions using solvent and an acid/base catalyst or refluxing the nucleophile and the Michael acceptor in a reaction flask is called as classical method for Michael addition.

Non-classical method: This method includes greener methods microwave irradiation, sonication with or without catalyst.

3. Sonication Assisted Michael Addition Reactions

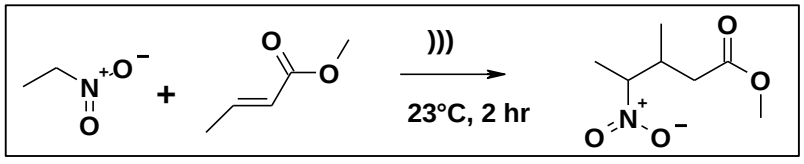
3.1 Literature Survey:

The Michael reaction is one of the most efficient methods for effective carbon-carbon bond formation and has wide synthetic application. These reactions are classically carried out in a suitable solvent in the presence of strong bases. The reactions suffer major drawbacks of long reaction time or yield or environmental concern.

Bergbreiter et al.[5] have reported the Michael addition of nitroalkanes to unsaturated carbonyl compounds was completed within 2 h under stirring using KF/ basic alumina catalyst.

The synthesis of chalcones catalyzed by KF/alumina good yield under sonication conditions.[6]

Michael Addition of Nitro Alkanes to α, β-Unsaturated Carbonyl Compounds: (scheme**1**)

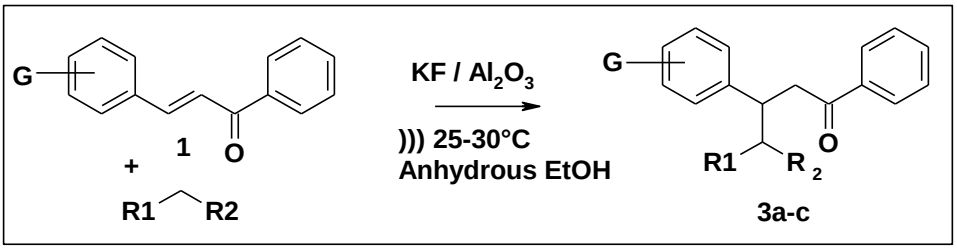


Scheme 1

All this has prompted to study the possibility of various Michael type reactions.

The Michael Reaction Catalyzed By Kf/ Basic Alumina Under Ultrasound:

In this reaction, chalcone (1) (1mmol), active methylene compound(2) (1.1 mmol), KF/basic alumina(145 mg) and anhydrous ethanol(2 ml) were added in a pyrex flask. The mixture was irradiated in the water bath of an ultrasonic cleaner. Progress of the reaction is monitored by TLC. The mixture was dissolved in CH_2Cl_2 and the solvent was evaporated under reduced pressure to give a solid.[7] The crude project was subjected to chromatography on silica gel eluted with pet ether/ ether. (Scheme **2**)



Scheme 2

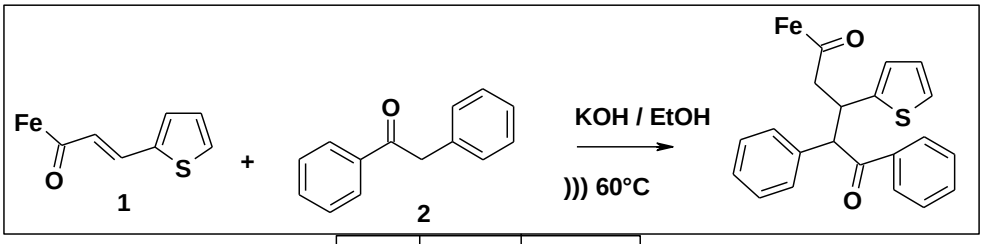
Table 1: showing the results for different reactions

Entry	**1.(G)**	**R_1**	**R_2**	**Time (min)**	**Product**	**Yield %**	**(Lit)**
A	H	$COOC_2H_5$	$COOC_2H_5$	10	3a	93	95 in 8hr
B	p-Cl	$COOC_2H_5$	$COOC_2H_5$	10	3b	90	90 in 8hr
C	p-NO_2	H	NO_2	120	3c	90	73 in 45 hr

An Efficient Synthesis Of Ferrocenyl Substituted 1, 5-Diketone:

Michael reaction of deoxybenzoin (2) or dibenzyl ketone with Ferrocenyl substituted chalcones (1) catalyzed by NaOH under Ultrasound can afford corresponding Michael adducts with excellent yields.[8] Further it has been seen that on changing the base to LiOH or KOH can accelerate the reaction rate to much extent. (Scheme **3**)

1,5 diketones are very important intermediate in organic synthesis due to their applications as fundamental starting materials in the preparation of many heterocyclic and polyfunctional compounds. This reaction under sonication offered an economic and faster way to synthesize them.

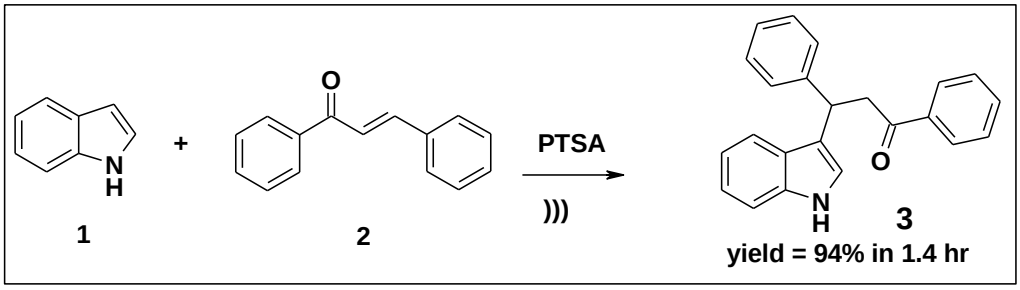


Base	yield	time
KOH	88%	30 min
NaOH	81%	2hr

Fe – Ferrocenyl Scheme 3

p-Toluenesulfonic acid Catalyzed Michael Addition To Synthesize β-Indolylketones Using Ultrasound

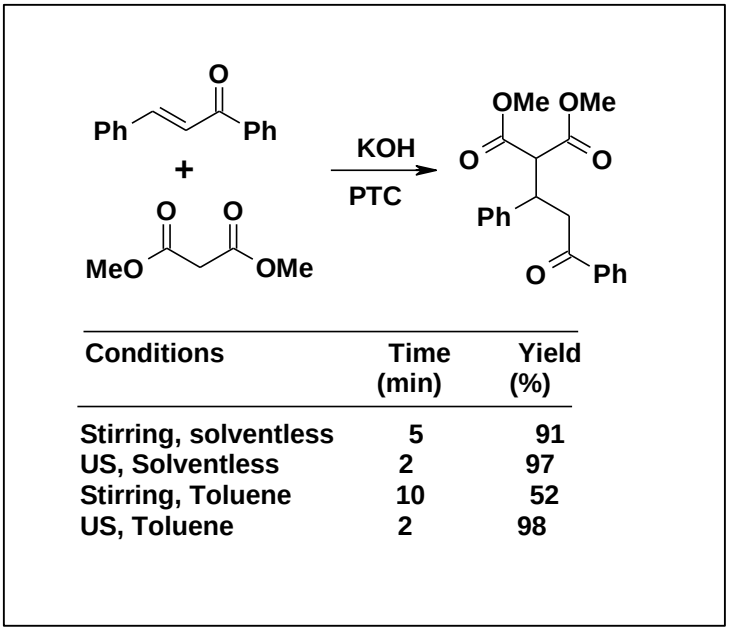
p-Toluenesulfonic acid has shown remarkable catalytic activity as a cheaper catalyst in ultrasound accelerated Michael reactions of indole (1) with α, β-unsaturated ketones (2) in the presence of anhydrous ethanol which provides one of the most important routes to the synthesis of β-Indolylketones (3).[9] Later are the building blocks for the synthesis of many natural products and other biologically active compounds. Previous methods of their synthesis require long reaction times, strong acidic conditions, and expensive reagents and also the yields of the reaction were very low. (Scheme **4**)



Scheme 4

Simple Michael Addition of β-Keto Esters or Di Keto Compound to α, β-Unsaturated Carbonyl Compounds:

Effects of ultrasound in solvent and solventless conditions. (Scheme **5**)



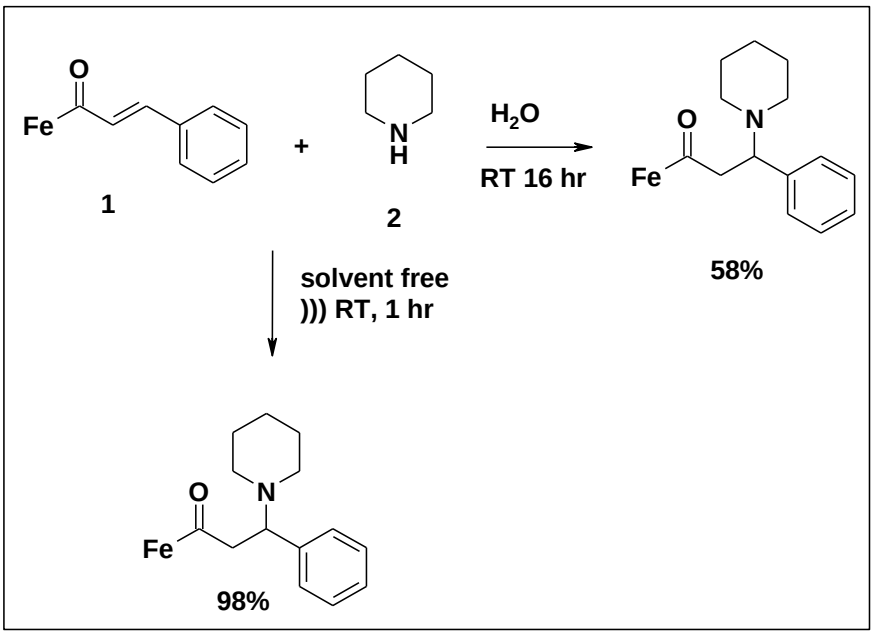
Conditions	Time (min)	Yield (%)
Stirring, solventless	5	91
US, Solventless	2	97
Stirring, Toluene	10	52
US, Toluene	2	98

Scheme 5

Ultrasound Mediated Michael Addition of Amines to Ferrocenylenones under Solvent Free and Catalyst Free Conditions:

A facile Michael addition of ferrocenylenones with aliphatic amines under ultrasound in the absence of solvent and catalyst at room temperature can afford 1- ferrocenyl-3- amino carbonyl compounds rapidly in high yields, which is also efficient in the aza Michael reaction of other α,

β-unsaturated carbonyl compounds such as chalcones, carboxylate esters, etc.[10] Reaction under existing methods does not proceed or take place in low yields after a long reaction time.
(Scheme **6**)

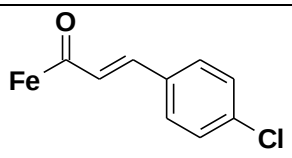
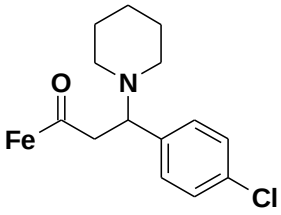
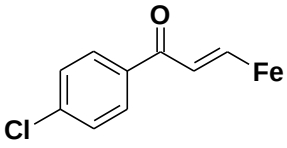
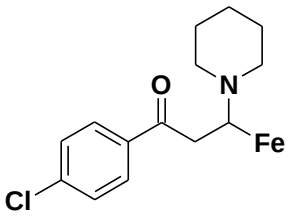
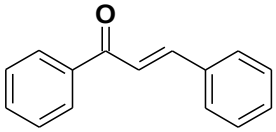
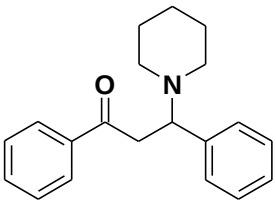
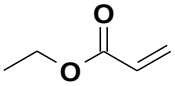
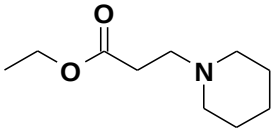
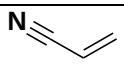
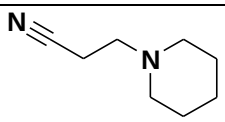


Scheme 6

Similarly, Michael addition of piperidine and to α, β-unsaturated carbonyl compounds under solvent free condition was studied under solventless conditions and excellent yields were obtained. The results for such kind of Michael addition are shown in Table 2.

This reaction offered a new synthetic methodology using ultrasound for the intermolecular aza Michael addition. In contrast to existing methods this technique is very efficient, general, simple, high yielding environmental friendly and moisture tolerant. Therefore it is novel entry for the synthesis of β- amino carbonyl compounds.

Table 2: Showing results of addition of piperidine to α, β-unsaturated carbonyl compounds

Entry	Unsaturated compound	Product	Time (hr)	Yield (%)
1			0.5	98
2			2	83
3			0.5	99
4			0.5	98
5			0.5	98

Cerium(IV) Ammonium Nitrate (CAN) Catalyzed Aza- Michael Addition of Amines To α, β-Unsaturated Electrophiles

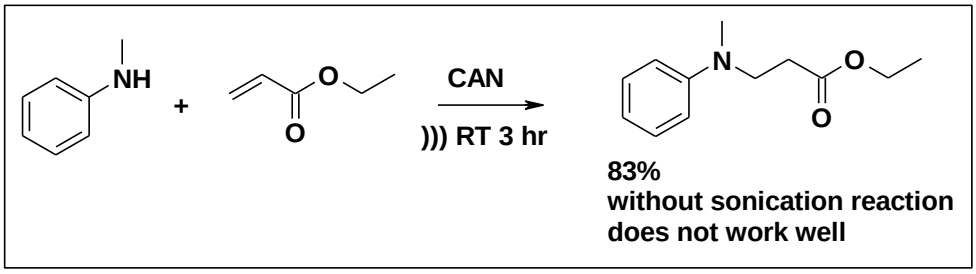
CAN Catalyzed facile and efficient aza-Michael addition of aromatic and aliphatic amines with α, β-Unsaturated Electrophiles in the absence of solvent under ultrasound irradiation.[11] The aza

Michael reaction provides an easy and direct route to β- amino esters. Such addition reactions require basic conditions or acidic catalysts. In order to overcome these limitations various procedures has been employed.

Very recently, Rao and coworkers reported β- Cyclodextrin promoted aza Michael addition of aryl amines.[12] In these reactions an equivalent amount of recyclable catalyst was added.

CAN is readily available, cheap, less toxic easy to handle and has profound reactivity with solubility in organic solvents. The can catalyzed aza Michael addition of amines include high yield, ambient temperature and solvent free condition.

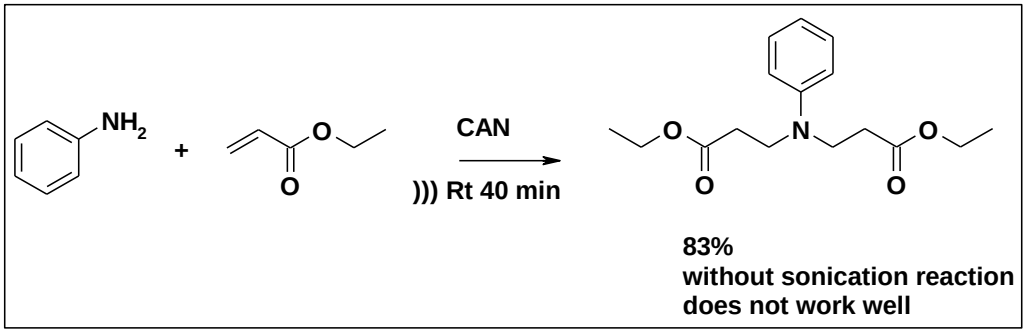
When a secondary aromatic amine, N- methylaniline, with ethyl acrylate and catalytic amount of CAN was sonicated at room temperature, a faster reaction occurred to give sonicated product in 83 % yield. (Scheme **7**)



Scheme 7

Similarly, aliphatic primary amines gave disubstituted products exclusively while primary aromatic amines selectively reacted with one or two molecules of ethyl acrylate. (Scheme **8**)

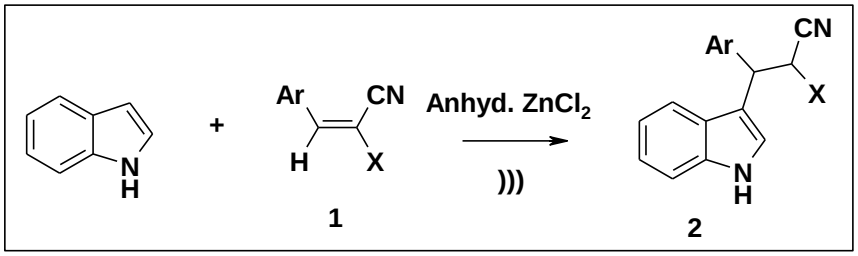
The reactions were also performed with piperidine, imidazol and good yields were obtained.



Scheme 8

An Efficient and Practical Synthesis of 2-((1H-indole-3-yl)(aryl)methyl)malononitriles under Ultrasound Irradiation:

Synthesis of 2-((1H-indole-3-yl) (aryl) methyl) malononitriles via Michael Addition of indole with various arylmethylene malononitriles was carried out in good yields using anhydrous Zinc chloride as catalyst under ultrasound irradiations.[13] (Scheme **9**)



Scheme 9

The results obtained in terms of yield and reaction time for various Ar and X are illustrated in Table 3 as follows:

Table 3

Entry	1		Time (hr)	Yield (%)
	Ar	X		
a	**3-ClC_6H_4**	**CN**	**1.5**	**95**
b	**2-ClC_6H_4**	**CN**	**1.5**	**97**
c	**4-ClC_5H_4**	**CN**	**1.5**	**96**
d	**4-ClC_5H_4**	**CO_2Et**	**6**	**94**

By this method good yield of product was obtained however in the absence of ultrasound product obtained was only 42%. Also it was found that 1.0 mmol of anhydrous catalyst gave the best yield. This reaction may prove a excellent methodology as the indole derivatives are found in various natural products, drugs etc.

4. Objective

Sonication Assisted Aza-Michael Addition to Acrylonitrile under Neat and Catalyst Free Conditions

Based upon above literature survey we did Sonication Assisted Aza-Michael Addition to Acrylonitrile under Neat and Catalyst Free Conditions. We have succeeded in developing a convenient and a greener method for the reaction under solvent free and catalyst free condition. Our method for Michael addition falls under the category of non-classical method. The methodology does not employ any direct heat to the reaction. The reaction time is also very less as compared with the other classical and non classical methods; it proceeds at room temperature without producing any of side products and hence giving excellent yields.

4.1 Aza-Michael Addition Reaction

Introduction

Interest in developing environmentally benign and solvent free reactions has increased dramatically. Consequently it has turned the attention of organic chemists for the development of such Synthetic methodology. The Michael reaction and its modified form such as Aza-Michael, Thio-Michael and Carba-Micheal reaction is one of the most exploited reactions in organic chemistry [14]. The β-amino esters/ketones/nitriles are useful synthons for the preparation of several nitrogen containing bioactive natural products [15], antibiotics [16] and chiral auxiliaries [17]. Besides this, a large number of biologically active compounds contain β-amino-ketone or ester moiety [18]. The development of novel synthetic methodologies for the preparation of these compounds is an attractive area of research in synthetic organic chemistry. Although β -amino ketones can be prepared by classical Mannich reaction [19], it has several drawbacks, such as, harsh reaction conditions, longer reaction time etc. Therefore, a variety of methods appeared in the literature for the synthesis of β-amino ketones, esters or nitriles [20]. Among the different synthetic methodologies, one of the most frequently used is the conjugate addition of amines to α β-unsaturated ketones or esters or nitriles, which is termed as aza-Michael reaction [1]. In general, the aza-Michael reaction requires a basic condition [21] or some special reaction condition [22]. However, in some cases, use of stoichiometric amount catalysts with reactive substrates results

several side reactions [23]. As a result, a wide variety of catalysts have been cited in the literature and in particular various Lewis acid catalyzed reactions have been carried out to minimize shortcomings [24]. Despite their usefulness, many of these procedures often require large amount of reagents, prolonged reaction time, drastic reaction condition and stoichiometric amount of Lewis acid catalyst such as $AlCl_3$, $TiCl_4$ and $SnCl_4$. This reaction has also been investigated using catalysts such as lanthanum trichloride ($LaCl_3$) [25], bromodimethylsulfonium bromide, [26] silicasupported perchloric acid, [27] cerium(IV) ammonium nitrate (CAN), [28, 29] β-cyclodextrin, [30] zirconium(IV) chloride, [31] samarium(III) triflate, [32] $ZrOCl_2.8H_2O$ on montmorillonite K10, [33] N-methylimidazole, [34] amberlyst-15, [35] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), [36] bismuth (III) triflate, [37] cadmium chloride ($CdCl_2$), [38] $Y(NO_3)_3$ $6H_2O$, [39] and cellulose supported copper(0). [40] However, there are various limitations with the reported methodologies, especially when using aromatic amines, such as long reaction times, low yields for aromatic amines, use of halogenated solvents, difficulty in recovery of high-boiling solvents, high temperatures, requirement of special efforts for preparation of the catalysts, use of costly catalysts, and moderate yields. Therefore, development for an alternative method which can overcome these limitations is always welcomed.

We have made an attempt to develop an environmentally greener method for such an important Michael addition reaction.

The scheme:

Scheme-10

In this thesis we are disclosing our finding on Aza-Michael addition of amines to α β-unsaturated compound acrylonitrile under solvent free and catalyst free conditions. (Scheme **10**)

5. Experimental Procedure

5.1 Materials Used:

The various amines used for the reaction are Morpholine, Diethanolamine, Ethanolamine, Diethylamine, Ethylenediamine, Imidazole, Pyrrolidine, N- methylpiperazine. All these were obtained from Loba Chemie (India). Acrylonitrile was obtained from Loba Chemie (India). All these chemicals were used as received without any further purification or recrystallization.

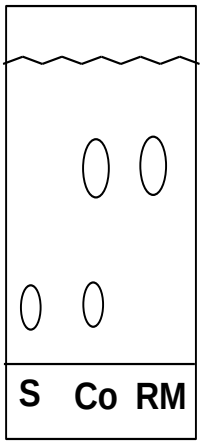
5.2 General Procedure:

In an initial experiment, acrylonitrile was allowed to react with Morpholine in an equimolar ratio in the absence of any solvent. It was observed that reaction proceeded mild exothermally with excellent yield of the Michael adduct at room temperature. Following similar reaction condition a series of aza-Michael adducts have been prepared using a diverse range of amines which is summarized in Table 4.

In 100 mL Round bottom flask equipped with different amines (1eq) was added acrylonitrile(1eq) drop wise with stirring manually. The reaction mixture was then sonicated for given time. The reaction was monitored by TLC. On completion of reaction the reaction mixture was concentrated under reduced pressure in a rotary evaporator to give the Michael adduct in given yields. The reaction of pyrrolidine, Ethylenediamine and Diethylamine was very exothermic.

TLC:

The reaction mixture was diluted with dichloromethane and spotted on freshly coated silica plate with co-spotting of reaction mixture and starting amines as shown below. For all the products of the reaction the TLC was run in 5% and 10% methanol in chloroform system. For all the reactions the spot of the product was observed to be nonpolar as compared with the different amines. General TLC is shown below



S - Starting material

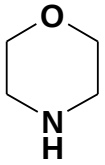
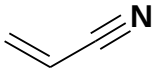
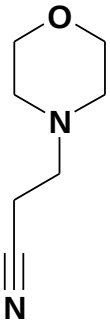
Co - Co-spotting of starting and reaction mixture

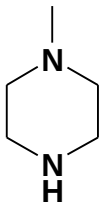
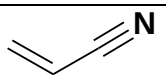
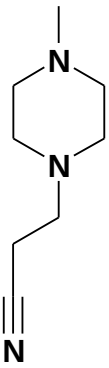
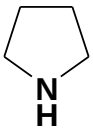
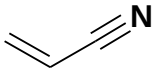
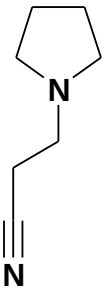
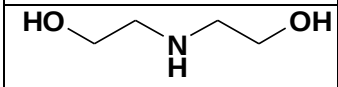
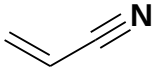
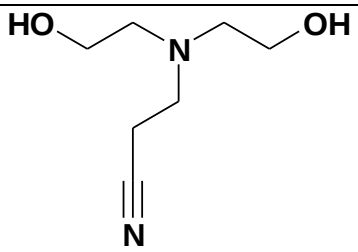
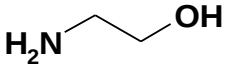
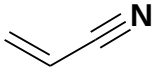
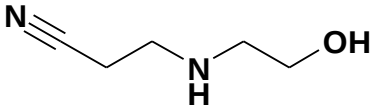
RM - Product or reaction mixture

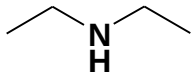
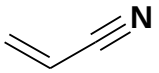
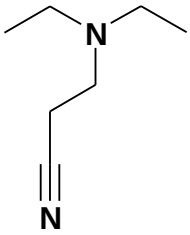
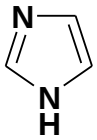
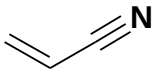
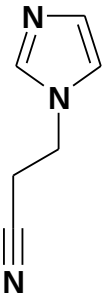
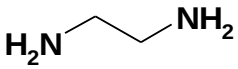
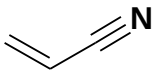
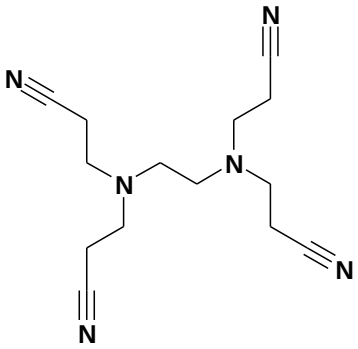
6. Results & Discussions:

The Aza Michael addition of various amines enlisted above was done to acrylonitrile. The product obtained, yield and reaction time is summarized in table 4.

Table 4

Amine	α, β - unsaturated compound	Product	Reaction time	Yield (%)
 **Morpholine**		 **3-Morpholino propanenitrile**	**4.5hr (US)* Followed by 1hr stirring**	**80**

 **N-Methylpiperazine**		 **3-(4-Methylpiperazin-1-yl) propanenitrile**	**3 hr (US)** **Followed by 1hr stirring**	**85**
 **Pyrrolidine**		 **3-(Pyrrolidin-1-yl) propanenitrile**	**10 min (US)**	**99**
 **Diethanolamine**		 **3-(Bis(2-hydroxyethyl) amino propanenitrile**	**4 hr (US)**	**96.6**
 **Ethanolamine**		 **3-(2-Hydroxy-ethylamino) - propionitrile**	**1.5 hr (US)**	**98.6**

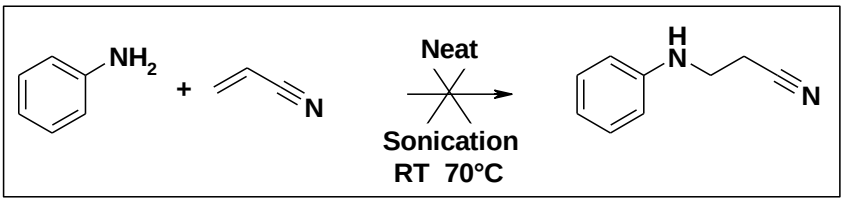
 **Diethyl amine**		 **3-(Diethylamino) propanenitrile**	**3 hr (US)** **Followed by1 hr stirring**	**82.9**
 **Imidazole**		 **3-(1H-imidazol-1-yl) propanenitrile.**	**4 hr (US)** **Followed by 2 hr stirring**	**92.8**
 **Ethylene diamine**		 **3-[{2-[Bis-(2-cyano-ethyl)-amino]-ethyl}-(2-cyano-ethyl)-amino]propionitrile**	**2.5 hr (US)**	**82**

Discussion:

In case of primary amines when one equivalent of acrylonitrile was used mono adduct was obtained while 2 equivalent gave di-adduct. Pure product could be obtained by concentrating the reaction mixture under reduced pressure. The main feature of this methodology is that no

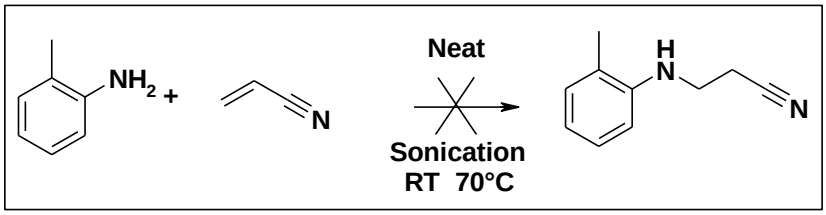
purification is required to obtain pure compound, therefore simple pure Michael adducts were clearly obtained in excellent yields.

Aromatic amines showed poor reactivity towards the Michael addition compared to aliphatic free amines, therefore the reaction of aniline on acrylonitrile failed. The reason for the failure is probably because the lone pair of electrons is involved in the ring and is not freely available for the Michael addition. For such reactions the use of catalysts is must. (Scheme **11**)



Scheme 11

In order to study the effect of electron donating group, the reaction was tried with o-Toluidine but reaction failed with it too. (Scheme **12**)



Scheme 12

7. Reactions using classical method:

The reactions were performed using classical method for the Michael addition reaction.

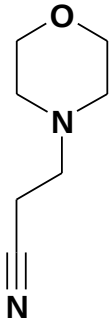
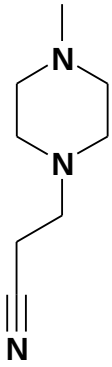
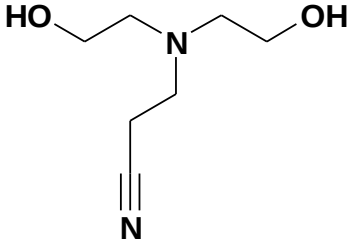
7.1 Procedure:

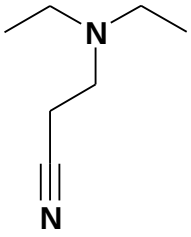
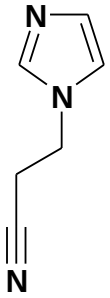
To a stirring solution of different amines in toluene/THF was added an equivalent of acrylonitrile. The reaction mixture was refluxed for a given time. The reaction was monitored on TLC. On reaction completion the reaction mixture was concentrated under reduced pressure in a rotary evaporator to obtain different Michael adducts.

7.2 Comparison of Classical & Non Classical Method for Aza Michael Addition:

Following table 5 shows the comparison of Aza-Michael addition under classical and non classical method. The products obtained were compared on TLC with the authentic products obtained by non-classical method. Identical products have same R_f values which were practically observed for the products obtained by both classical and non-classical methods. This table also gives a glimpse of benefits of a convenient and greener sonication method for the reaction over the classical method.

Table 5 showing the comparison of classical and non classical methods for aza Michael addition:

Product	Reaction time in classical method	Reaction time in non-classical method (US)	Yield classical	Yield non classical
	6 hr reflux at 80°C, in THF	Room temperature and neat	60.2%	80%
	7 hr reflux at 80°C, in THF	Room temperature and neat	65.5%	85%
	3 hr reflux 100°C in toluene	Room temperature and neat	72.7%	96.6%

	**5 hr reflux at 60°C in THF**	**Room temperature and neat**	**60.1 %**	**82.9%**
	**6 hr reflux at 60^0C in THF followed by overnight stirring with acidic alumina as catalyst**	**Room temperature and neat**	**50%**	**92.8%**

8. Spectral Analysis of Products:

FT IR spectra

IR spectrum in the range of 4000-400 cm^{-1} was recorded on "Perkin Elmer" FTIR Spectrometer, from School of Physics and Material Science, Thapar University, Patiala. Software Origin Pro 7.5 was used to draw the curves and was fitted using the protocols available with the software.

^{1}H NMR Spectra

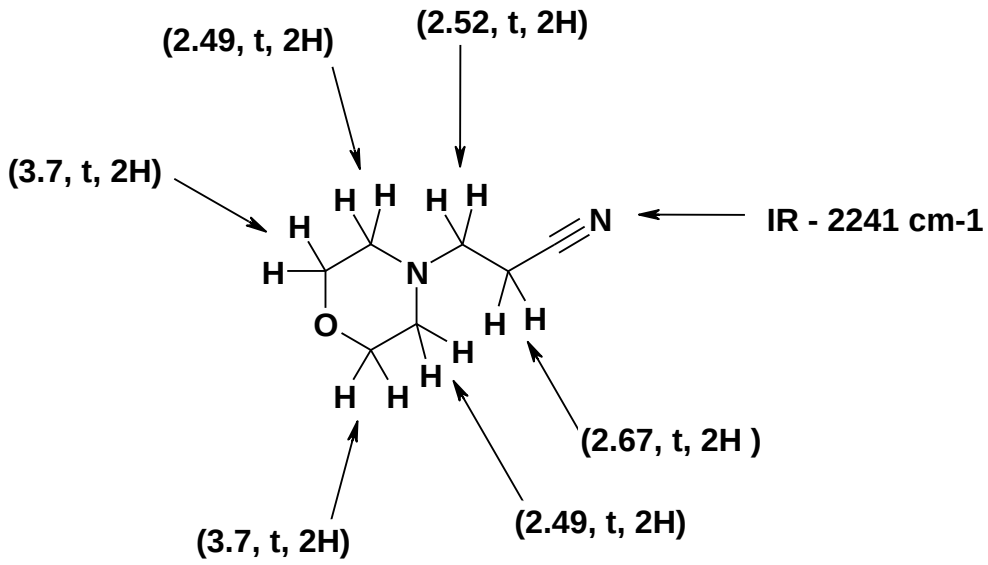
^{1}H NMR Spectra were recorded on 400 MHz FT-NMR Cryo-magnet Spectrometer (Bruker), from Sophisticated Analytical Instrumentation Centre (SAIF), Punjab University, Chandigarh.

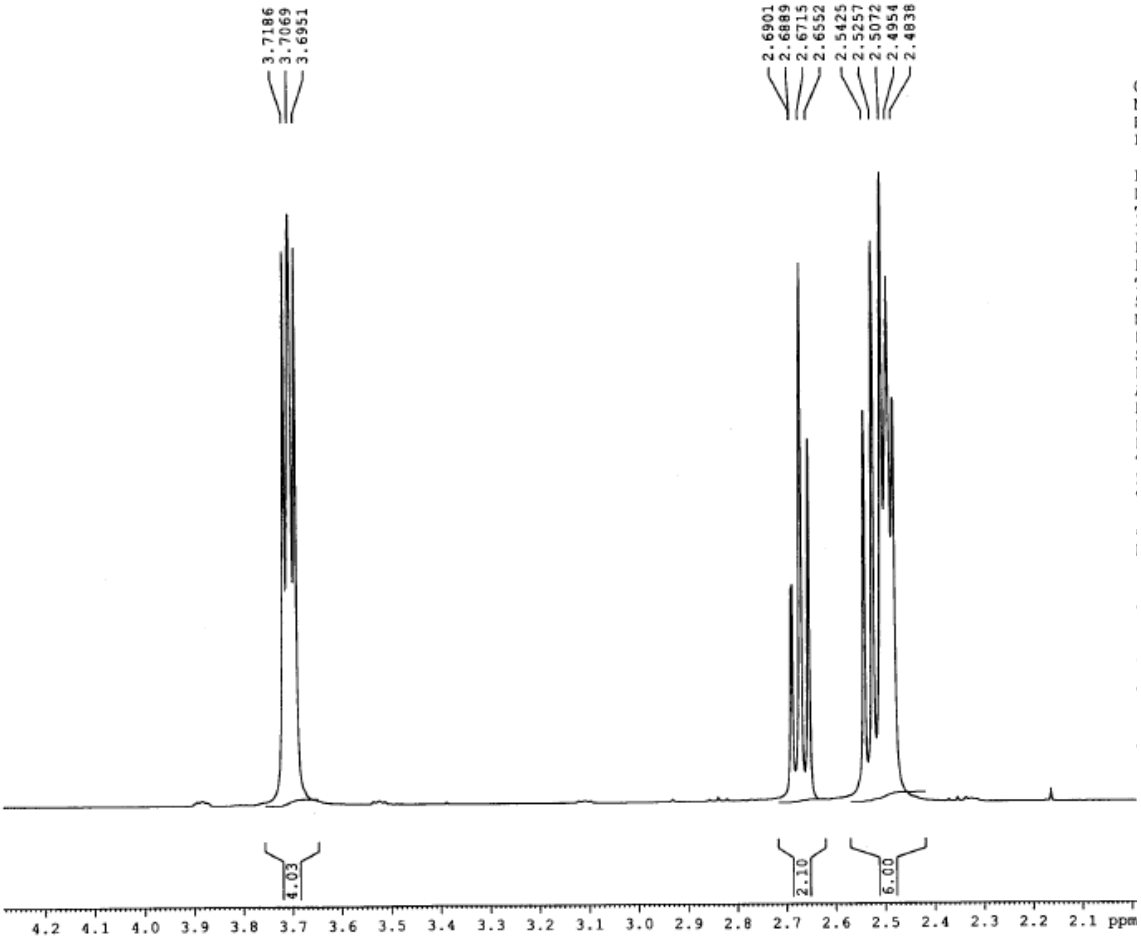
Mass Spectra

Mass spectra was recorded on Waters Micromass Q- Tof in positive ionization on electron spray ionization (Esi) method from Sophisticated Analytical Instrumentation Centre (SAIF), Punjab University , Chandigarh.

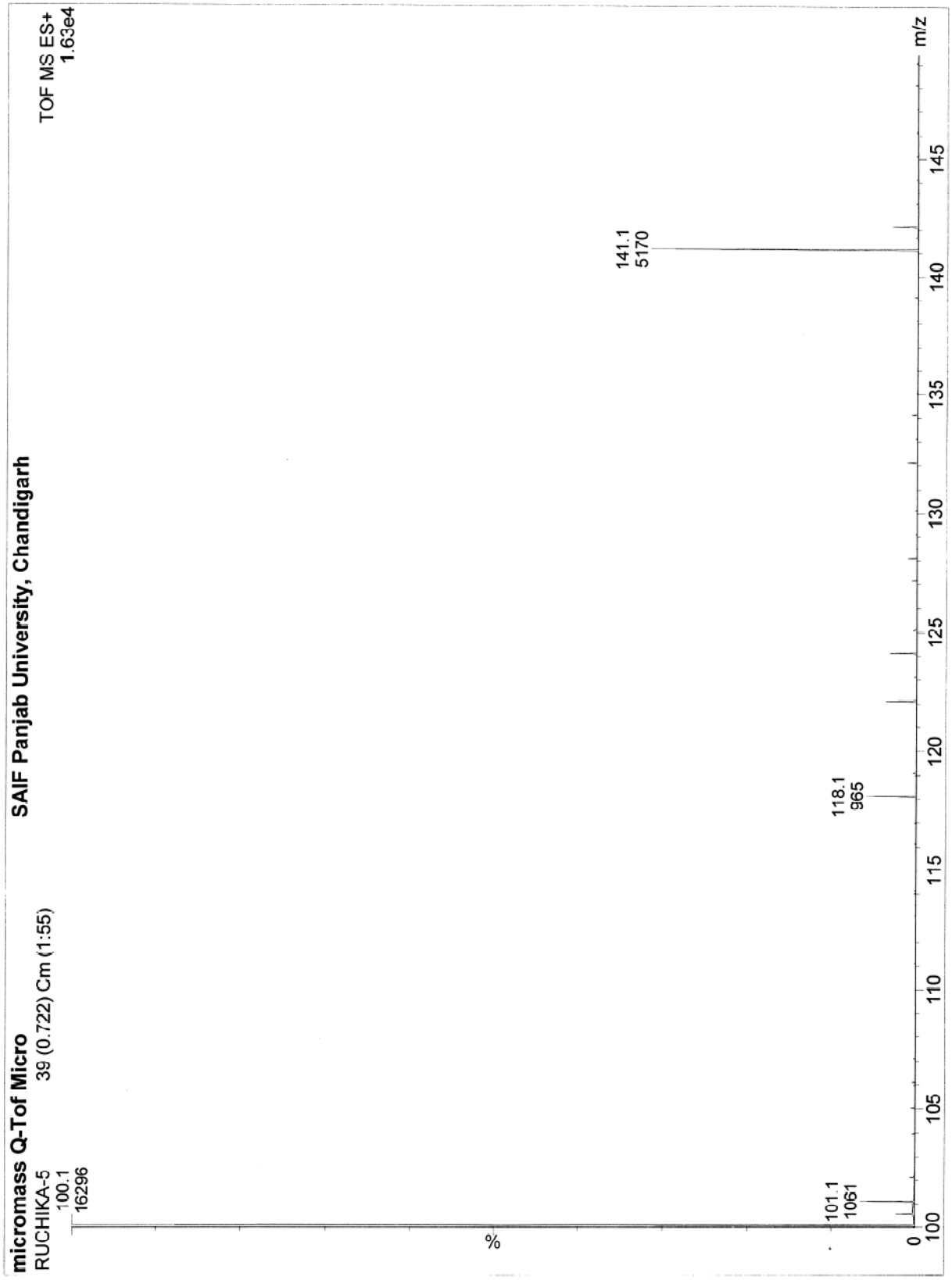
NMR Spectra of 3-Morpholinopropanenitrile:

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.49 (t, 4H), 2.52 (t, 2H), 2.67 (t, 2H), 3.70 (t, 4H)

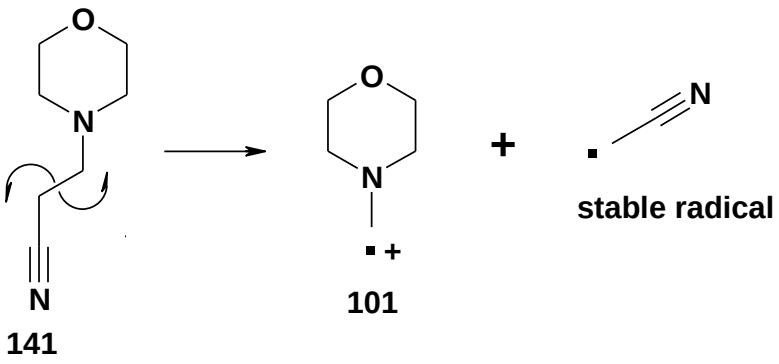




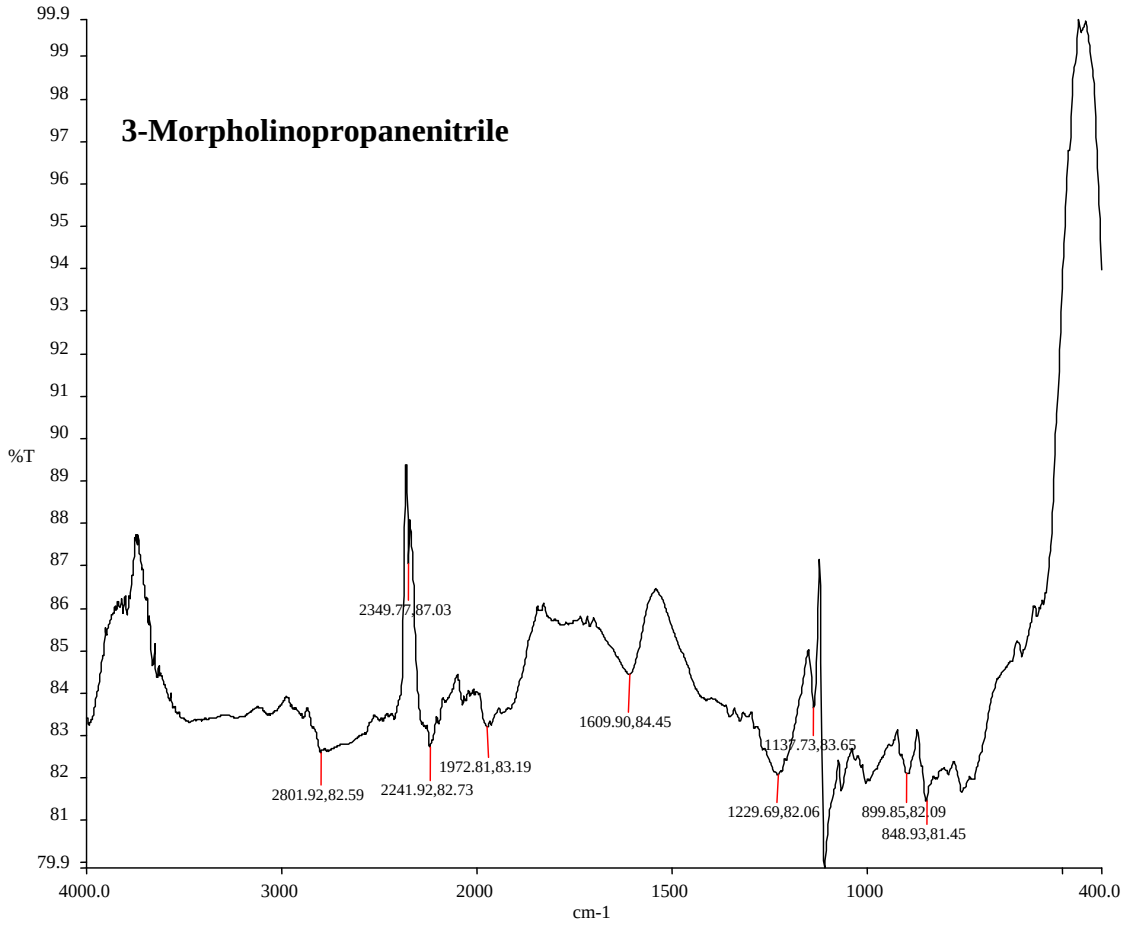
Mass Spectra of 3-Morpholinopropanenitrile (m/z): (M+H) 141



Mass fragmentation pattern:

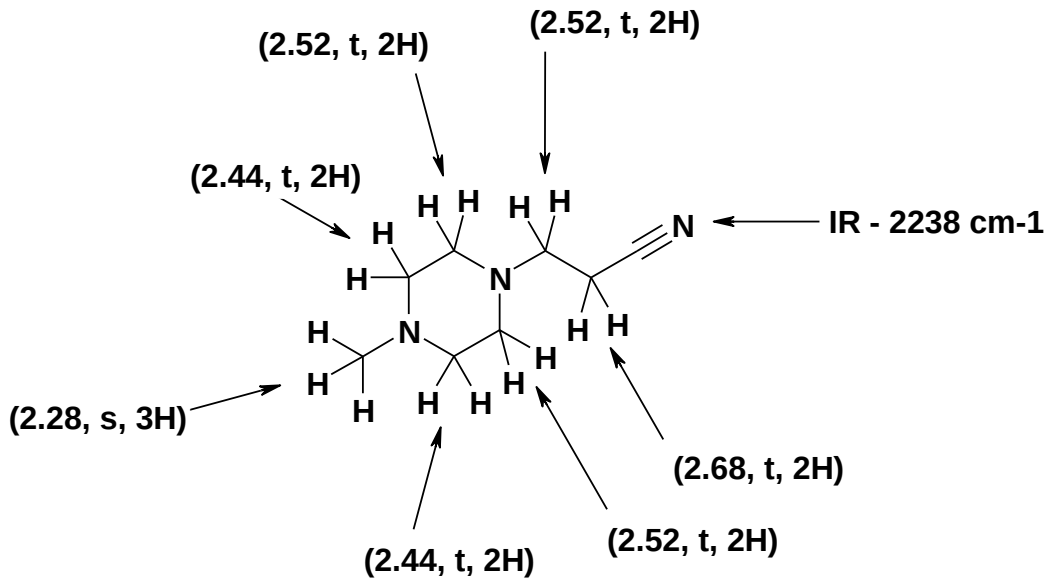


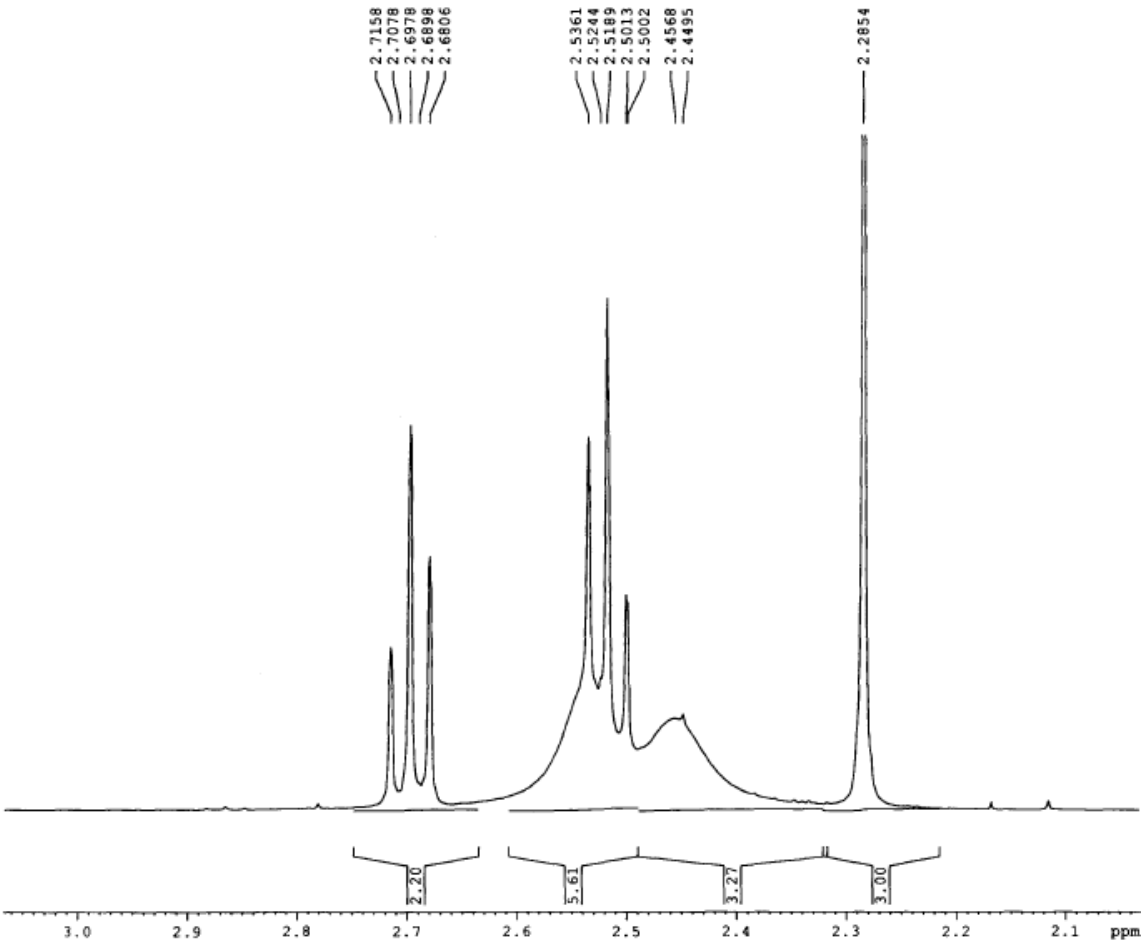
IR -spectra– 2241 cm^{-1} CN group frequency



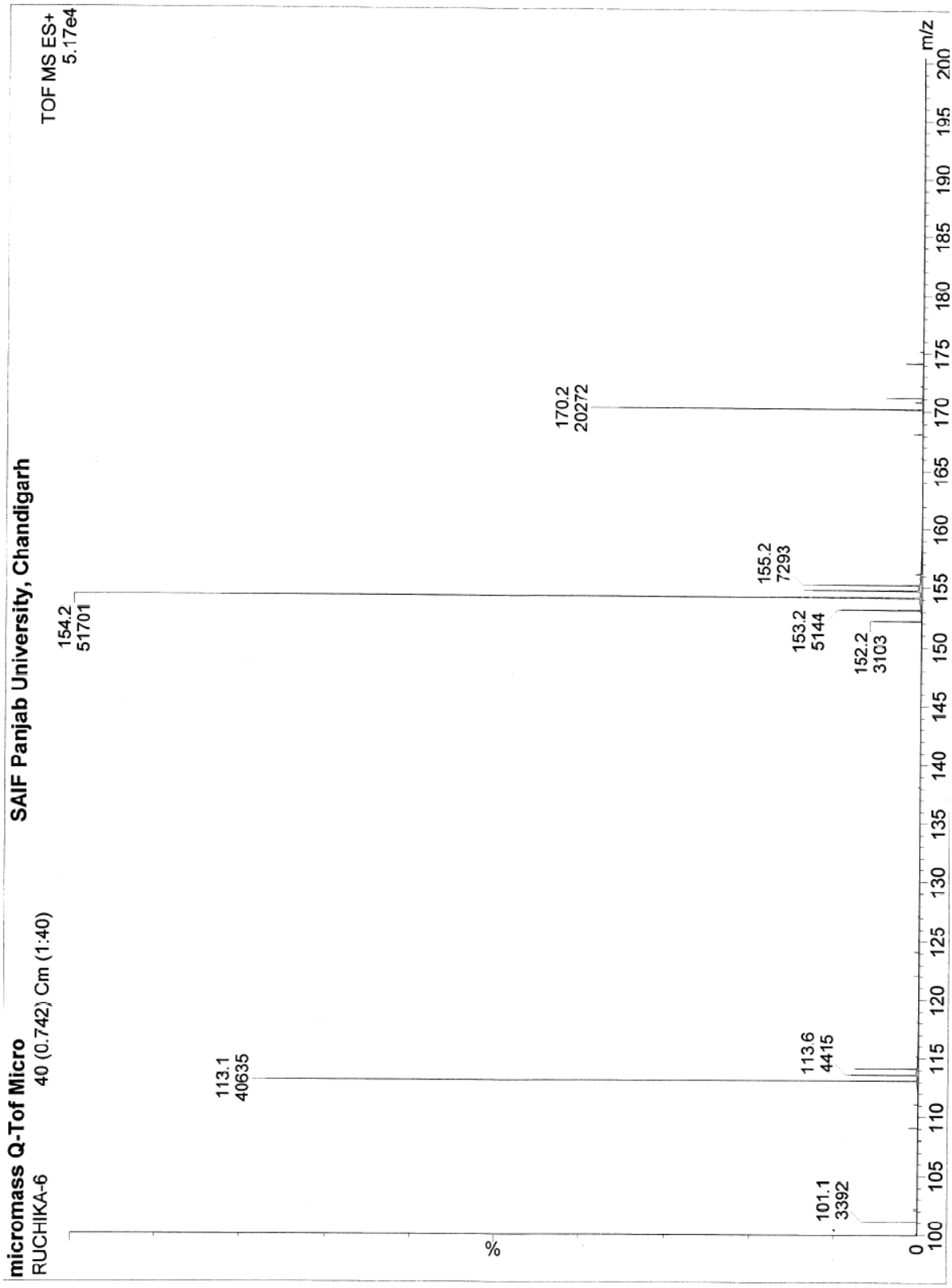
NMR Spectra of 3-(4-Methylpiperazin-1-yl)propanenitrile:

^{1} H NMR (400 MHz, $CDCl_3$) δ: 2.28 (s, 3H), 2.44 (t, 4H), 2.52 (t, 6H), 2.69 (t, 2H).

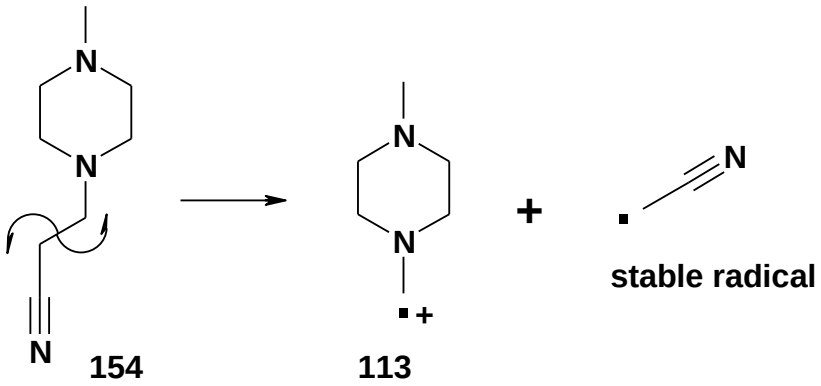




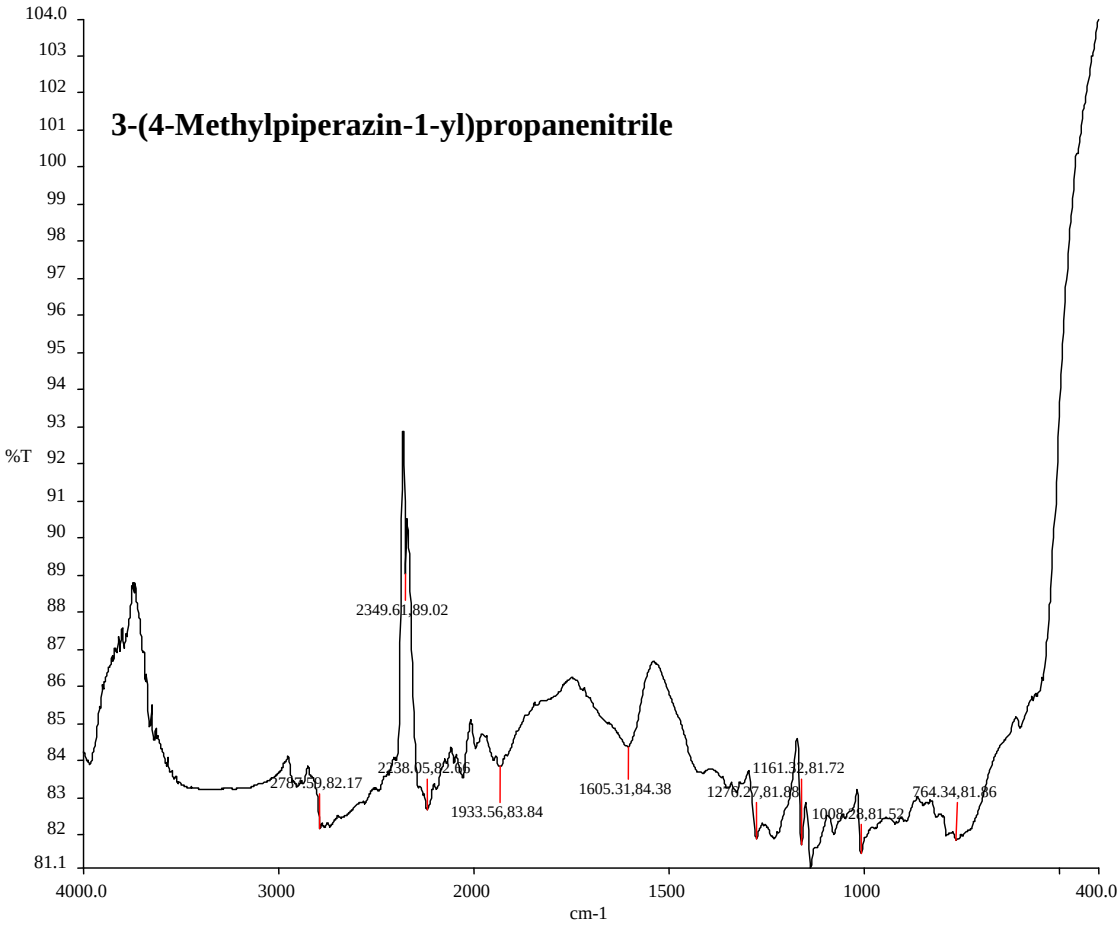
Mass Spectra of 3-(4-Methylpiperazin-1-yl)propanenitrile (m/z): (M+H) 154



Mass fragmentation pattern:

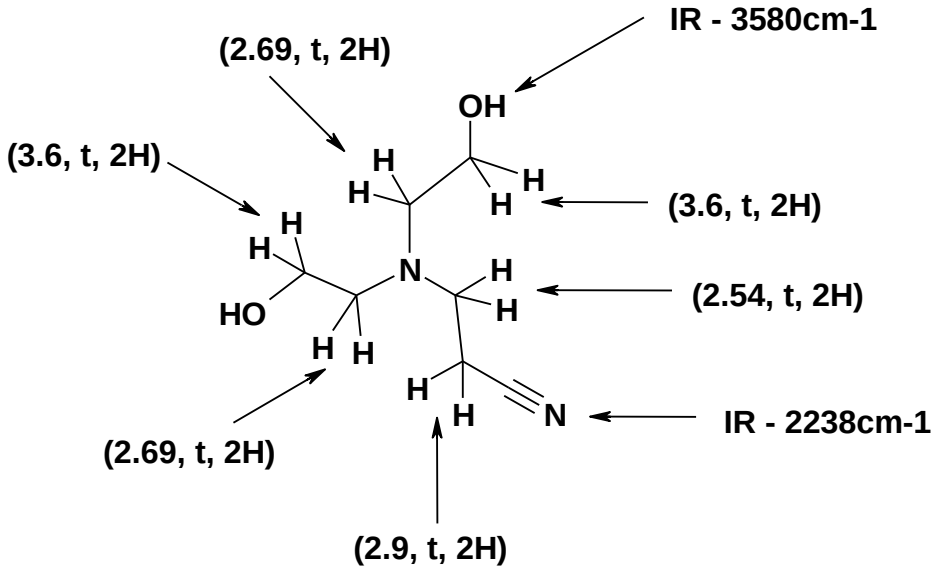


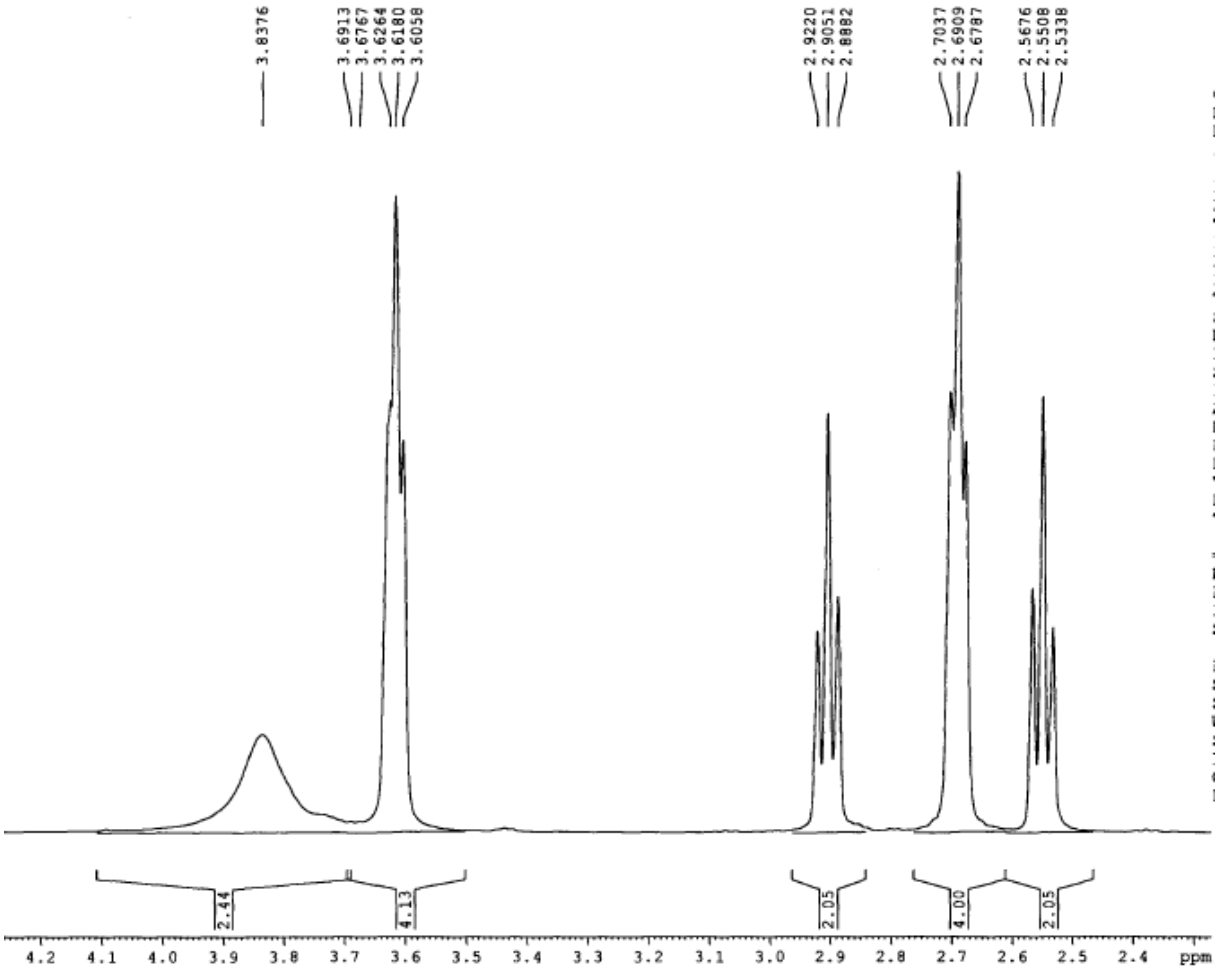
IR – spectra 2238 cm^{-1} (CN):



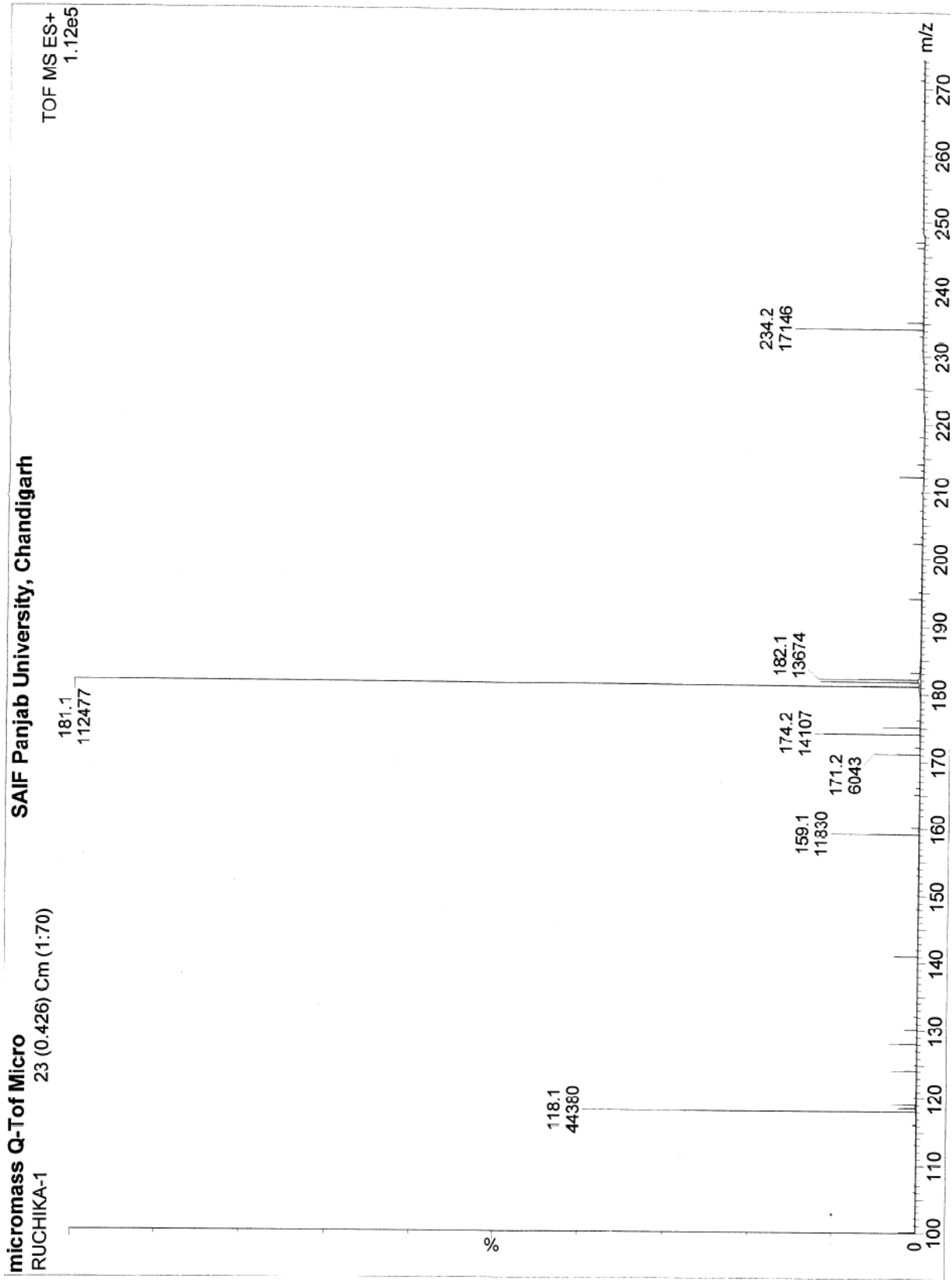
NMR Spectra of 3-(Bis(2-hydroxyethyl)amino)propanenitrile:

[1] H NMR (400 MHz, CDCl3) δ: 2.54 (t, 2H), 2.69 (t, 4H), 2.9 (t, 2H), 3.6(t, 4H).

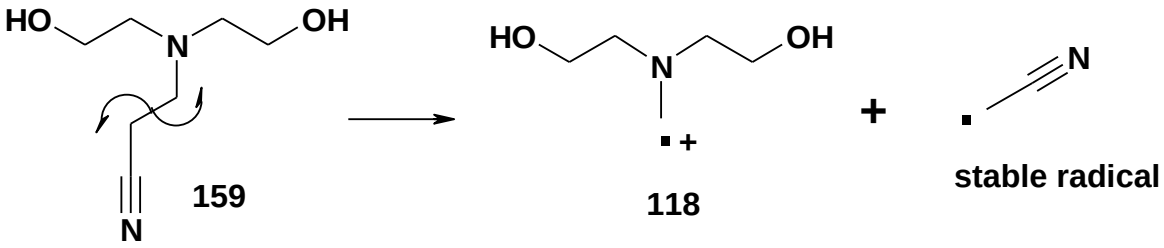




Mass Spectra of 3-(Bis(2-hydroxyethyl)amino)propanenitrile: (m/z): (M+H) 159.



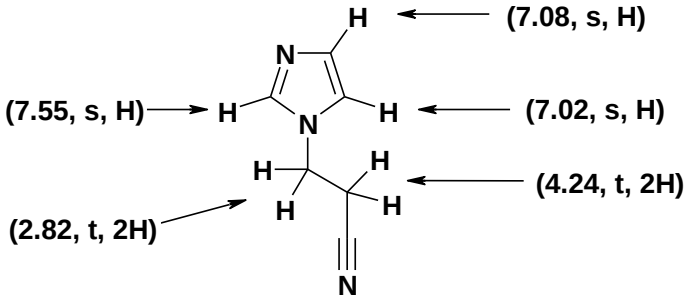
Mass fragmentation pattern:

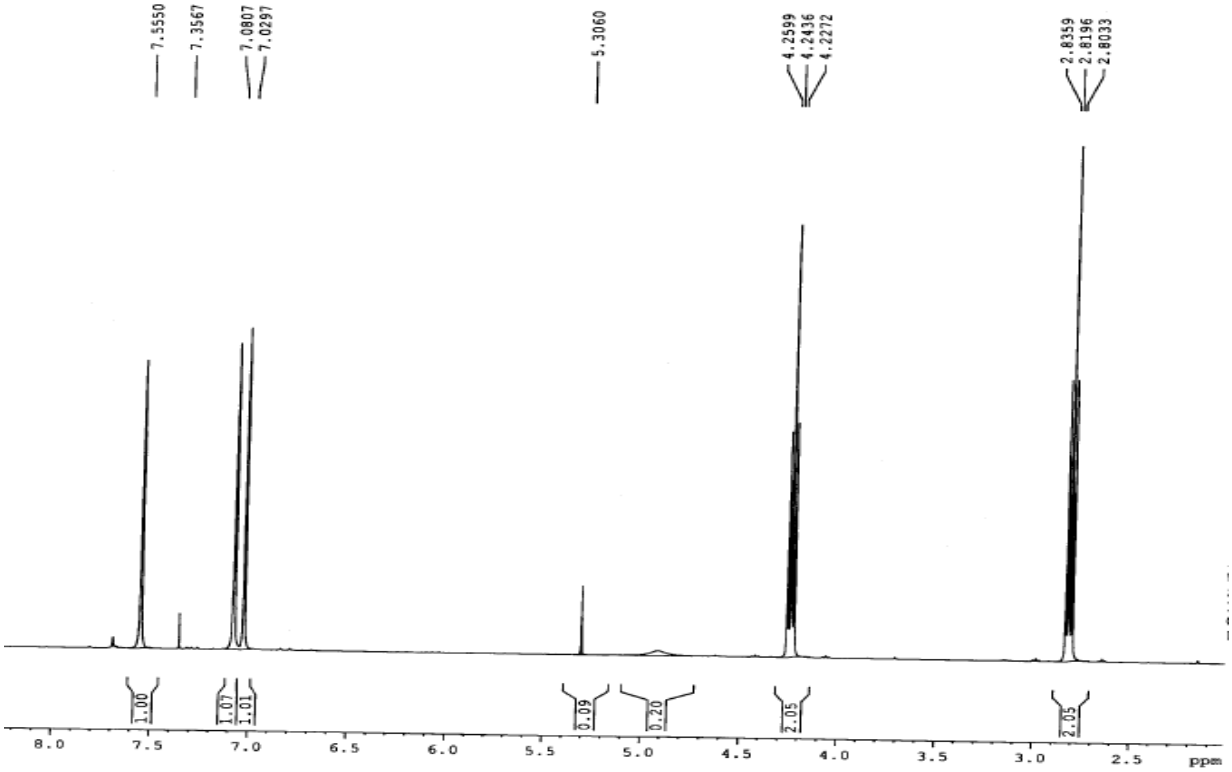


IR – (frequency cm^{-1}) 2238 cm^{-1} (CN), 3580 cm^{-1} (OH)

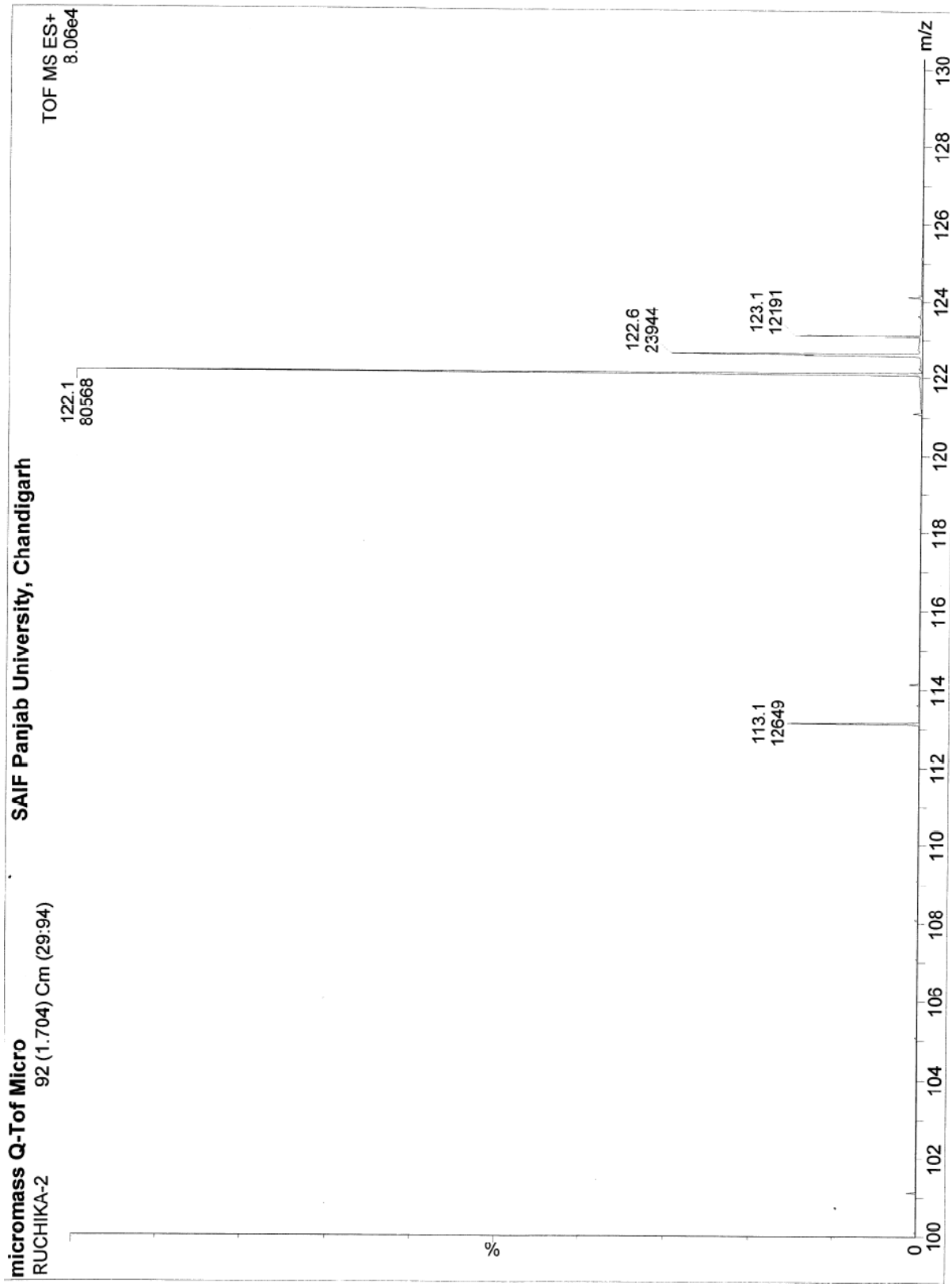
NMR Spectra of 3-(1H-imidazol-1-yl)propanenitrile:

^{1} H NMR (400 MHz, DMSO d^{6}) δ: 2.82 (t, 2H), 4.24 (t, 2H), 7.02 (s, 1H), 7.08 (s, 1H), 7.55 (s, 1H).



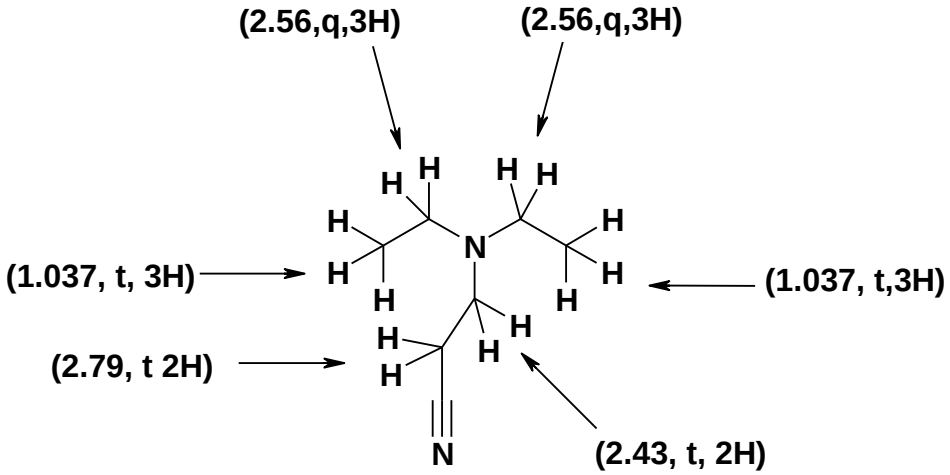


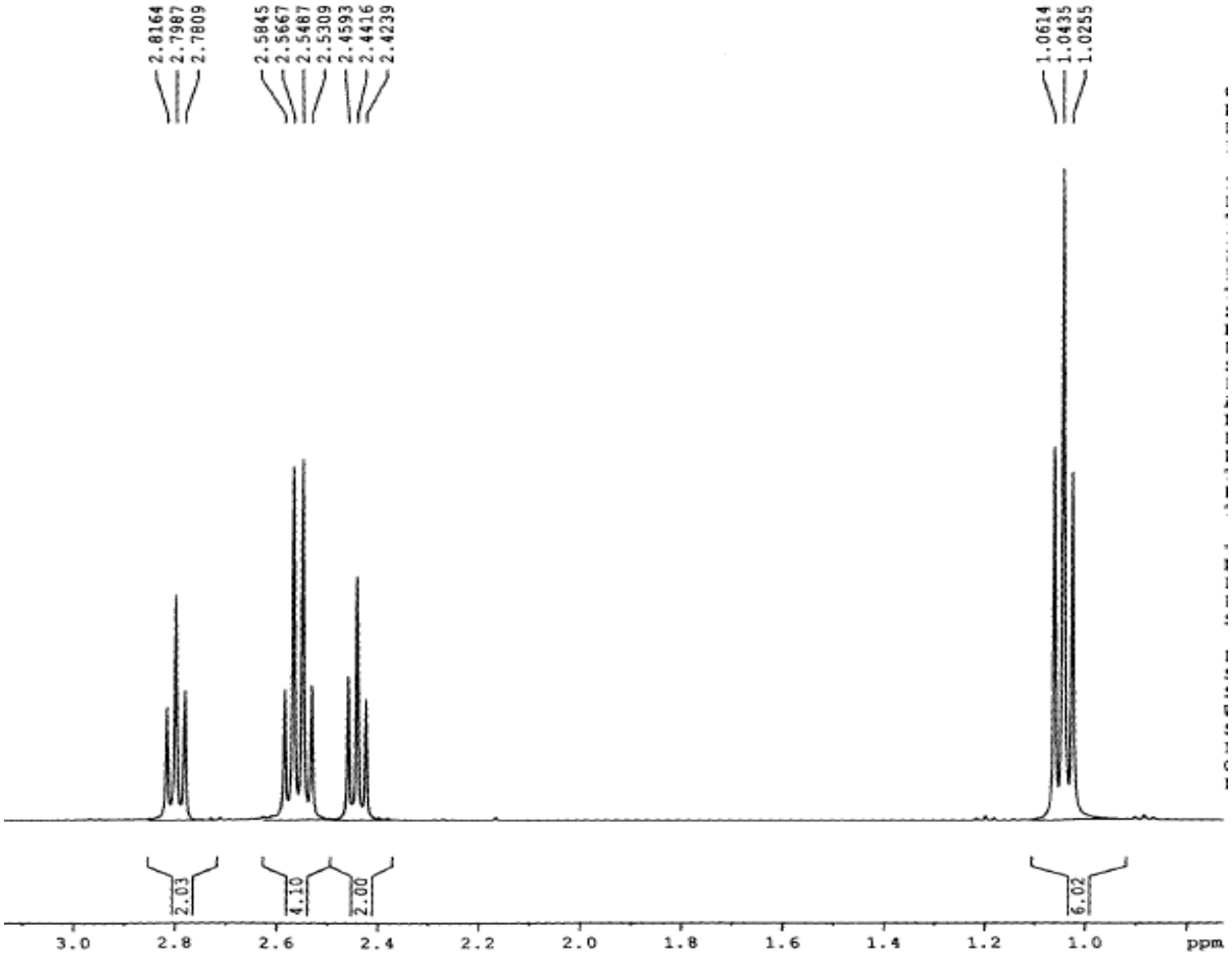
Mass Spectra of 3-(1H-imidazol-1-yl)propanenitrile (m/z): (M+H) 122.



NMR Spectra of 3-(Diethylamino)propanenitrile:

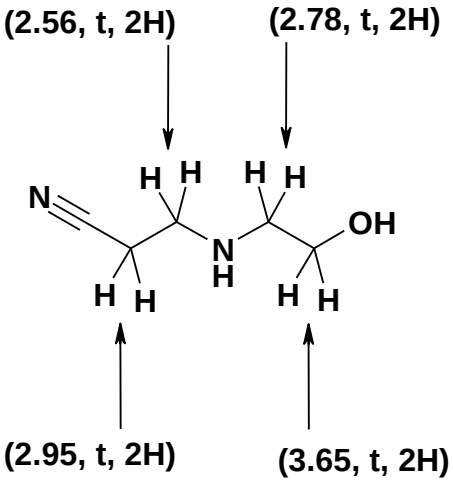
^{1} H NMR (400 MHz, $CDCl_3$) δ: 1.037 (t, 6H), 2.43 (t, 2H), 2.56 (q, 4H), 2.79 (t, 2H).

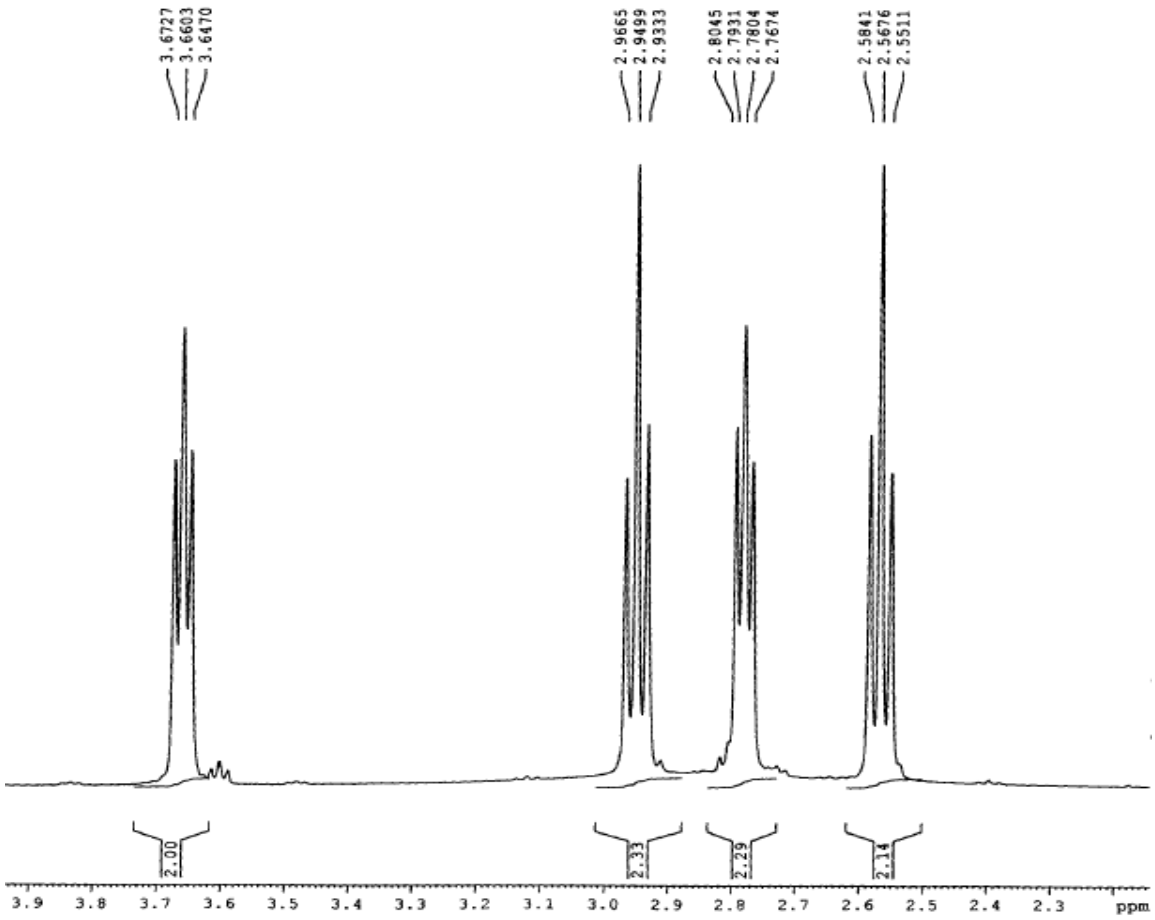




NMR Spectra of 3-(2-Hydroxyethylamino)propanenitrile:

^{1} H NMR (400 MHz, $CDCl_3$) δ: 2.56 (t, 2H), 2.78 (t, 2H), 2.95 (t, 2H), 3.65 (t, 2H).





Conclusion:

Our finding about the Aza-Michael addition is that the studied reactions proceeded under solvent free conditions and without any catalyst which is not reported earlier. The reaction proceeds smoothly with different primary and secondary aliphatic amines while the reaction fails with aromatic primary amines in which the lone pair of electrons on nitrogen is involved in conjugation e.g. aniline compounds. For the reaction of aromatic amines with β-unsaturated compound (acrylonitrile) different catalysts can be employed as reported in the literature. The reaction condition developed by us is a green method for the aza Michael addition reaction. It is also advantageous over the classical method in terms of yield and reaction time. Moreover, it also eliminates the use of hazardous solvents, purification and crystallization.

Future scope for Aza-Michael addition reaction:

As we have developed a novel method for the aza Michael addition reaction in this thesis, future scope in this field is to apply this method for aza Michael addition on different α, β –unsaturated compounds besides acrylonitrile such as α, β –unsaturated esters (example: methyl acrylate) α, β –unsaturated ketones (example different chalcones) and α, β –unsaturated nitro compounds. The scope of this method also lies in testing reactions of different nucleophiles on Michael acceptors under neat and solvent free conditions.

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