CHAPTER-4

ONION EXTRACT MEDIATED NOVEL SYNTHESIS OF PYRAZINE

IV.1. Pyrazine

Diazine is described as a compound with monocyclic aromatic ring having two nitrogen atoms with a molecular formula of $C_4H_4N_2$. The three isomers of diazine are pyridazine, pyrimidine and pyrazine (Figure IV.1). Pyrazine or more commonly known as 1,4- diazine, can be taken into consideration as aromatic in character and their chemistry has very little in common with benzene although their resonance energy is lower than benzene. Pyrazine display inductive resonance properties (Figure IV.2) and manifest the weakest basicity among diazine compounds, even weaker than pyridine. This is due to the electron withdrawing effect of nitrogen atoms that is positioned at *p*-position (Sato, 2014). The specific dissociation constant for pyrazine are pKa1= 0.65 and pKa2= - 5.78 (Dolezal & Zitko, 2015).

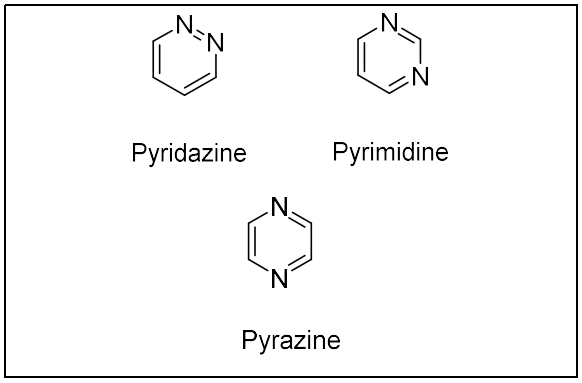


Figure IV.1. Three isomers of diazine.

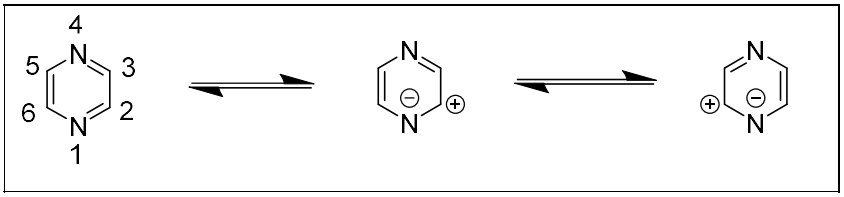


Figure IV.2. Inductive resonance property of pyrazine.

Pyrazine is stable, discoloured compound and its dipole moment is zero. The boiling point and the melting point of pyrazine are 116°C and 54°C respectively. Most of the lower homologues are liquids at room temperature which the lower members of the series are very soluble in water whereas several are miscible in all proportions. From an x-ray study, it was found that the ring is planar and the carbon-carbon distance is longer than benzene which is 1.40Å.

IV.2. Variety of application

Pyrazine is a momentous compound that have found manifold applications as pharmaceuticals. Pyrazines are exigent components of aroma fragrances [1], potential pharmacophore of a large number of biologically active substances [2-6], and widely used as agrochemicals [7-9]. Pyrazine derivatives are also used as relaxing cardiovascular and uterine smooth muscle, antithrombotic, anti-aggregation, COX-2 inhibiting, and analgesic effects [10], anticancer as well as anti-inflammatory activities [11].Some important derivatives are given bellow **(**Figure IV.3).

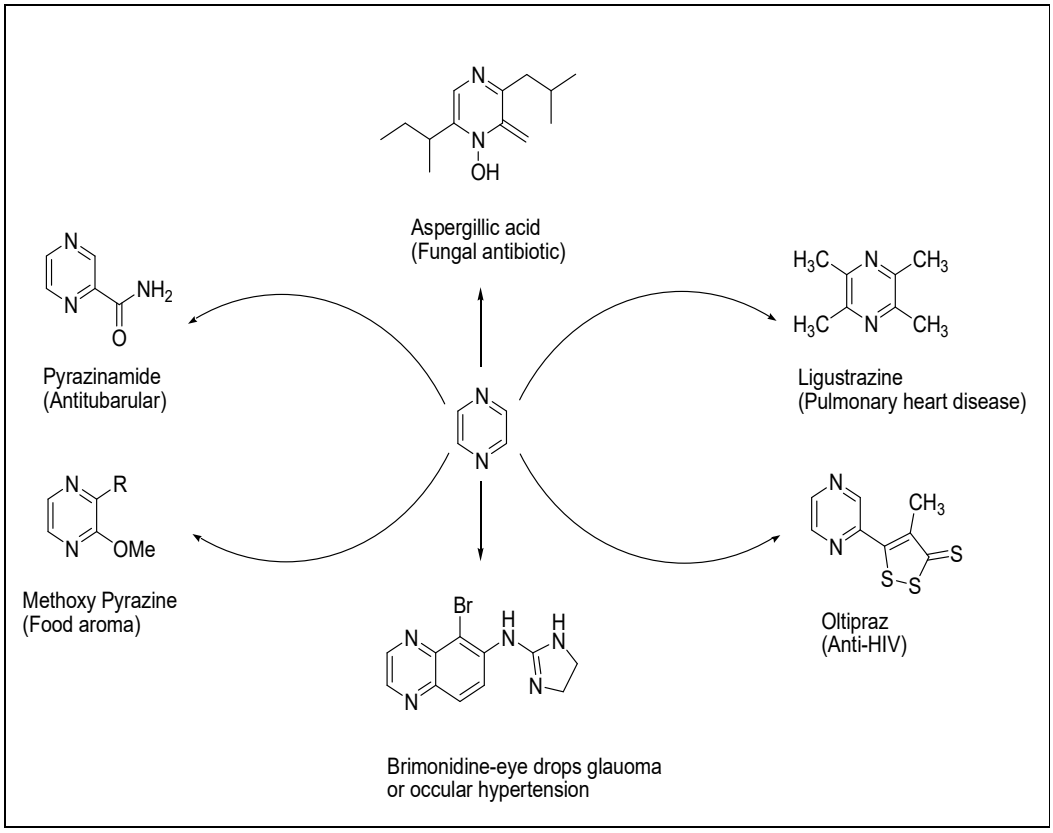


Figure IV.3. Examples of some bioactive Pyrazine derivatives.

They act as an odor signal to repel predators and effectively prevent vegetative tissue or immature fruit from being eaten [12] .That's why pyrazines find various applications as ingredients in pesticides, insecticides, dyes, and pharmaceutical compounds[13]. Pyrazines get attention from the food industry as important ingredients in raw and roasted foods. Especially alkylated pyrazines (Figure IV.4) are in the focus, as they have strong olfactory properties.

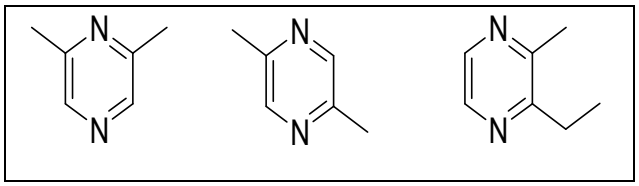


Figure IV.4. Some alkylated pyrazine used in food industries.

IV.3. Natural occurrences

Pyrazine are created naturally by living organisms such as plants [14], animals, insects[15], marine organisms as well as microorganisms[16]. Pyrazine compounds such as 2-methoxy-3-sec-butylpyrazine, 2-methoxy-3- iso-butylpyrazine, 2-methoxy-3-iso-propylpyrazine can be found in galbanum oil, beans, beetroot, lettuce, nasturtium and green pepper bell [17-18] .They can be extracted from potatoes, nuts, and coffee. Beside those compounds, pyrazine ring can be generally found in heat processed food as it is formed through Maillard reaction [19]. Allen and Lacey (1998) reported that 2-methoxy-3- isobutylpyrazine, 2-methoxy-3-secbutylpyrazine and 2-methoxy-3-isopropylpyrazine play significant role in the unique aroma of wine, especially the wine derived from grape. Apart from that, Woolfson and Rothschild (1990) reviewed that pyrazine acts as alerting pheromones, site markers, trail pheromones, repellent and escape pheromones for insects, bees as well as moths. Showalter et al. (2010) established that 2, 5-dimethyl-3(2-methylbutyl)pyrazine is the mandibular alarm pheromone excreted by fire ant Wasmannia auropunctata. Thus Pyrazine found ubiquitously in nature but only in relatively low content [20].

IV. 4. History of Pyrazine Synthesis

Laurent in 1844, first synthesized a new compound “amarone”, named by him. The “amarone” was prepared by dry distillation of α- phenyl-α-(benzylideneamino) acetonitrile, PhCH=NCHPhCN. It was later confirmed to be 2, 3, 5, 6-tetraphenylpyrazine in 1897 by Snape and Brooke (Figure IV. 5). [21]

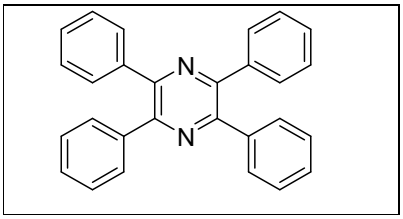


Figure IV. 5. 2, 3, 5, 6-tetraphenylpyrazine.

IV.5. Synthesis of Pyrazine

There are many synthetic viewpoints for the pyrazine ring and its derivatives. Ohtsuka et al.[22], Taylor and Dumas[23] synthesize pyrazine through cyclization process. In addition Büchi and Galindo[24] reported the regioselective formation of alkyl pyrazine via thermal electrocyclization aromatization path way. Beside this, Jones[25],Vogle and Taylor[26], Ohta et al.[27], Tazaki et al.[28], Zhang et al.[29] proposed condensation medthod to prepared pyrazine derivatives. Whereas Fukunaga and Begland[30] demonstrated that (4+2) cycloaddition also helpful to synthesize it. On the other hand Lee et al.[31], Itoh et al.[32], Richard[33], Park et al.[34], Latha et al.[35]tried their best to produce pyrazine derivatives by using metal catalyst.

Table IV.1. Some synthetic approachs of pyrazine derivatives.

Sl. No.	Reactants	Reagents /Catalyst	Solvent, Conditions	Product	Reported by (Year)
1	α-amino acid amides and 1,2-dicarbonyl	NaOH	MeOH	Pyrazine derivatives	Jones (1949)[25]
2	aminomalonamid amidine dihydrochloride and dry glyoxal bisulphate	dilute ammonium hydroxide	0-20°C	Pyrazine	Vogl and Taylor (1959)[26]
3	dicyanide with ammonia	-	MeOH	Pyrazine derivatives	Taylor and Dumas (1981)[23]
4	diiminosuccinonitrile with 1,2-dimethoxyethylene and ynamines	-	-	Pyrazine derivatives	Fukunaga and Begland (1984)[30]
5	diamine compound	copper-chromite catalyst	300-450°C	Pyrazine derivatives	Lee et al. (1990)[31]

6	allylamines and α-oximido carbonyl methyl chloroformate	potassium *tert*-butoxide	Toluene, 300°C	Pyrazine derivatives	Büchi and Galindo (1991)[24]
7	2,3- diamino-3-phenylthioacrylonitrile With glyoxal	m-chloroperbenzoic acid (MCPBA)	-	3-phenylthiopyrazinecarbonitrile	Tazaki *et al.* (1994)[28]
8	2,2-diethoxyacetophenone with 2,3- diamino-3-phenylthio-acrylonitrile	trifluoroacetic acid (TFA).	2-propanol, 22-24h	6-phenyl-3-phenylthio-pyrazinecarbonitrile	Zhang *et al.* (2001)[29]
9	isonitroso-acetophenone and aminoacetonitrile	$FeCl_3$, 10% Pd-C, H_2	MeOH, 50°C	Pyrazine derivatives	Itoh *et al.* 2002[32]
10	α-hydroxylketones and 1,2-diamino	MnO_2/ KOH-MeOH	CH_2Cl_2, Reflux, 90 mins.	Pyrazine derivatives	Richard (2003)[33]
11	propyleneglycol and ethylenediamine	CuO-ZnO-SiO2	360°C	2-methylpyrazine	Park *et al.* (2003)[34]
12	Two moles of ethylenediamine	copper oxide-copper chromite catalyst.	340-440°C	Pyrazine	Latha *et al.* (2007)[35]
13	1,2- diamine and 1,2-dicarbonyl	potassium *tert*-butoxide	RT, 6-8h	Pyrazine derivatives	Ghosh and Mandal (2012)[36]

14	*o*-phenylenediamine and benzil	*p*-toluenesulfonic acid (*p*-TSA) / ultrasonic wave	H_2O-EtOH	2,3-diphenylbenzopyrazine	Mahadik *et al.* (2014)[37]

IV.5.A. Formation of pyrazine through Maillard reaction

In addition to the previously mentioned methods, pyrazine can be synthesized by Louis-Camille Maillard (Nursten, 2005) or most commonly known as Maillard reaction[19]. The Maillard reaction is a non-enzymatic browning of food that involves condensation of carbonyl compound (reducing sugar) and amine (amino acid). Scalone et al. (2015) proposed that the general mechanism in producing pyrazine via the Maillard reaction starts with condensation of dicarbonyl compound (from degradation of reducing sugar) and amino acid. Strecker aldehyde and α-aminoketones were formed following decarboxylation of the condensed product through cyclic transition state. Then condensation of two molecules of α-aminoketones give dihydropyrazine. The dihydropyrazine could either go through oxidation to give pyrazine or deprotonation then combined with Strecker aldehyde to give another derivative of pyrazine (Scalone et al., 2015)[38].

IV.6. Importance of Onion

Common onion (Allium cepa L.) is one of the oldest cultivated plants, employ worldwide as both vegetable and flavouring. Onions are an important source of several phytonutrients as flavonoids, fructooligosaccharides (FOS), and thiosulfinates and other sulfur compounds, recognized as important elements of the Mediterranean diet [39]. The composition of the phytochemical may differ in accordance to geography, seasonal harvesting and processesing. Due to the presence of these phytochemicals, it has many applications in material chemistry [40–41] (Nanoparticle preparation) and medicinal field; including, anticancer, antiinflammatory, antiproliferative, reducing serum cholestereol, and blood pressure, immune stimulation, surgical scars, ability to modulate the detoxification system and free radical scavenging activity [42–50]. In fact, onions contain high levels of phenolic compounds, which have antioxidant properties besides beneficial effects against

different degenerative pathologies (cardiovascular and neurological diseases, dysfunctions based on oxidative stress) [51]. Flavonoids are the major phenolics in onions, which can be classified to different sub-group (flavones, flavanones, flavonols, isoflavones, flavanonols, flavanols, chalcones, and anthocyanins) on the basis of the degree of unsaturation and the degree of oxidation of the central ring. Flavonols are the most generous in onions, present as their glycosides, that is, quercetin and kaempferol [52, 53], in higher concentration (280–400mg/kg) than other vegetables (i.e., 100mg/kg in broccoli, 50mg/kg in apple) [54]. Anthocyanins, belonging to anthocyanidins, are mainly present in red onions (250mg/kg), besides having a composition rich inflavonols as yellow onions [55]. FOS represents another source of phytochemicals in onions bulbs. They are mostly inulin, kestose, nystose, and fructofuranosylnystose. The health benefits of these carbohydrates have been widely reported in the past years due to their prebiotic effect [56]. In onions, sulfur compounds are responsible for typical odour and flavour and are also active antimicrobial agents [57]; hence, onions may be used as natural preservatives to control microbial growth [57]. Furthermore, they have also protective effects against cardiovascular diseases.

IV.7. Organic synthesis catalyzed by onion extract

In the development of new synthetic and catalytic protocols in organic synthesis, the developments of environmentally benign and economical processes are highly demandable. One of the young catalysts is onion extract.

The precursors of sulfur-containing compounds in onion are S-alk(en)yl-L-cysteine sulfoxides (ACSOs, i.e., methiin, propiin, and isoalliin). 1-Propenyl-L-cysteine-sulphoxide (isoalliin, 1) is usually found in highest concentration and is responsible for the tearing and pungency associated with onions. When the onion is cut, the isoalliin (1) undergoes a series of rapid reactions. After the breakage of the tissue caused by cutting, enzyme Alliinase catalyzes the conversion of 1-propenylcysteine sulfoxide to (E)-1- propenesulfenic acid (2), which is then, rearranged to the volatile and highly reactive lachrymatory factor (LF) (Z)-propanethial S-oxide (5), which produces propionaldehyde (6), sulphuric acid (7) and hydrogen sulfide (8) [58]. Besides, onion extract contains water soluble phytochemicals- caffaeic acids, ferullic acid sinapinic acid, cyaniding, tannic acid and other organic acids. These factors responsible for the acidic nature of onion extract and make its pH 3.6 with the strength of 0.0034 N.

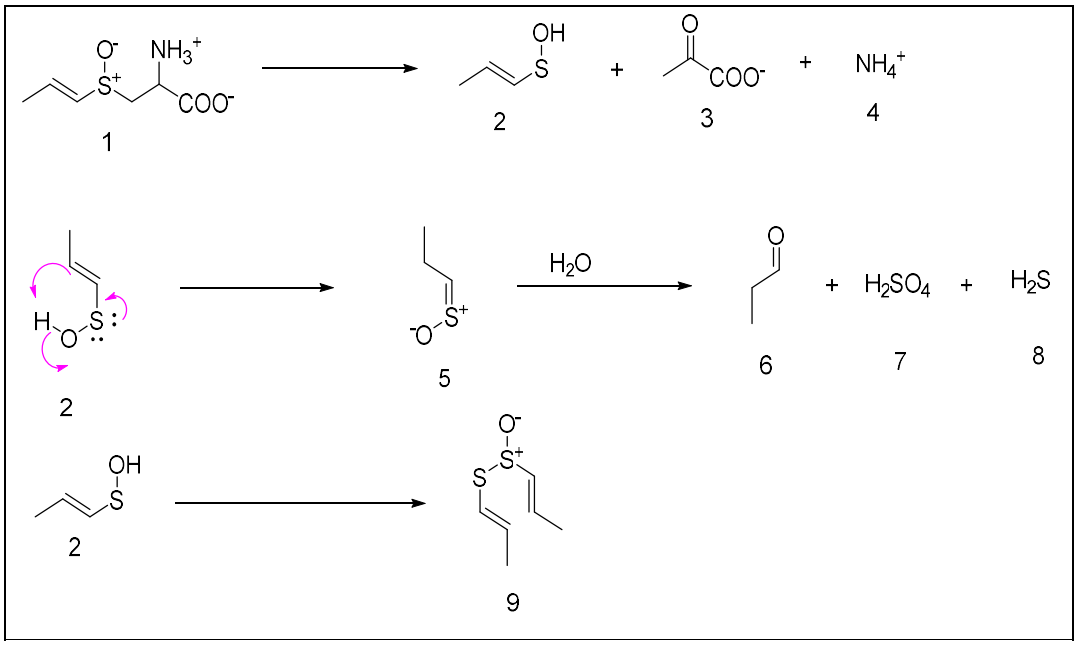
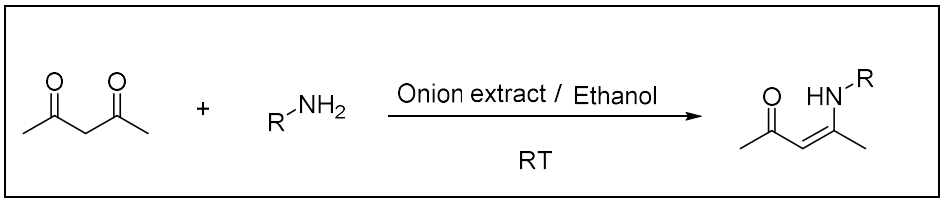


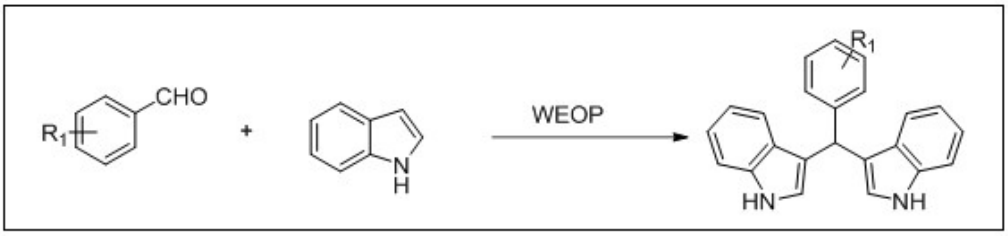
Figure IV.6. Pathway for the enzymatic synthesis of the lachrymatory factor propanethial-S-oxide (5) and for the spontaneous production of the flavour factor thiosulphinate (9), in onion. The lachrymatory factor propanethial-S-oxide (5) has two isomers, syn and anti. Both the isomers are formed, but the syn compound is formed preferentially.

Based on the above facts to avoid hazardous chemicals in recent years researchers utilized onion extract as a catalyst into some organic synthesis in different ways. In 2017, Kaliyan Prabakaran *et al.*[59] were reported the onion extract catalyzed method of synthesis of enaminones 3 and enaminoesters 5 from 1,3-dicarbonyl compounds and primary amines. The reaction was preceded smoothly in the presence of onion extract (0.01 mL) to afford enaminones and enaminoesters in good yields (Scheme IV.1).



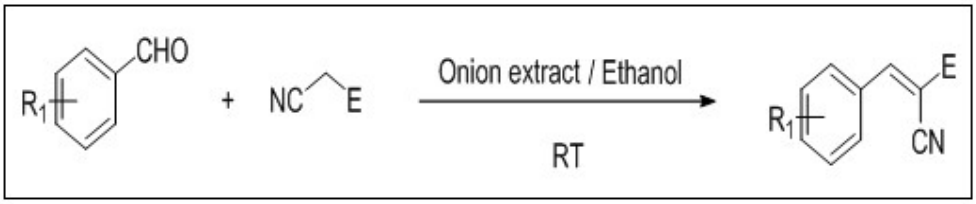
Scheme IV.1. General scheme for the synthesis of enaminone derivatives using onion extract. R = different functional groups.

In 2019, Poh Wai Chia *et al.*[60] demonstrated the synthesis of bisindolylmethanes (BIMs) using Water Extract of Onion Peel (WEOP) (Scheme IV.2).



Scheme IV.2. Synthetic route towards the preparation of bisindolylmethanes (BIMs) using WEOP. R_1 = different functional groups.

In 2019, again Kaliyan Prabakaran *et al*. [61] placed onion extract in a favourable light to catalyze Knoevenagel condensation reaction of active methylene compounds with various aldehydes such as aromatic, aliphatic, heterocyclic and α, β-unsaturated (Scheme IV.3).

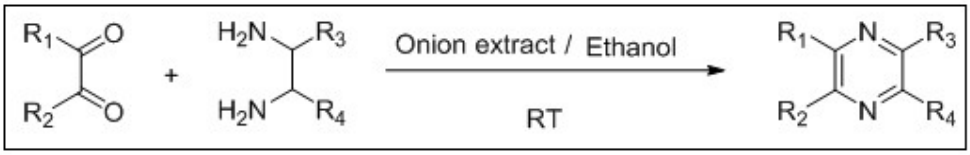


Scheme IV.3. General scheme for the synthesis of α-cyanoacrylonitriles and α-cyanoacrylates using onion extract.

Now, to explore the catalytic applicability of onion extract, worth of Pyrazine derivatives and to avoid the limitation of its synthesis, keeping these in mind, we report a simple and mild one-pot method for the synthesis of Pyrazine derivatives

IV.8. Present work

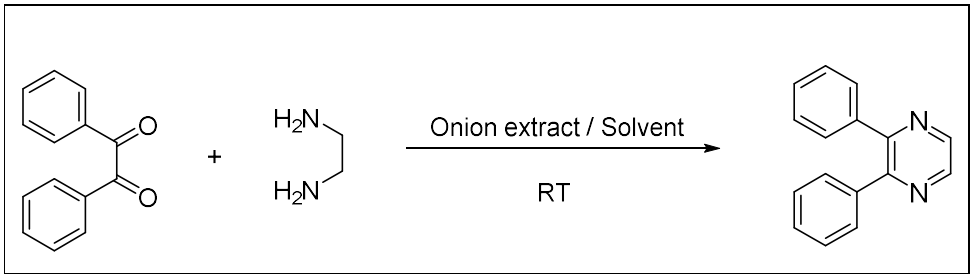
In the present work we report an efficient catalytic system for the synthesis of Pyrazine derivatives using extract of onion at room temperature is described. A very good to excellent yields in reasonably short reaction time, high atom economy, usage of readily available starting material, operational simplicity and easy workup are the fundamental features of this protocol.



Scheme IV.4. The general scheme and reaction for the synthesis of Pyrazine derivatives. R_1, R_2, R_3, R_4 are the different functional groups.

IV.8.A. Results and discussion

Our inaugural endeavor on this reaction, in order to earn a decent reaction condition, was made with the reaction of Benzil and Ethylenediamine in the attendance of onion extract under diversity of solvent systems for 45-90 minutes. It was found that, the method is efficient for all solvents with good yields. Here the greenest solvent, water could have been the first in this race, leaving every solvent behind, but its low ability to dissolve organic compounds did not allow him to do so (Table IV.2, entry 4). Our scheme also completes the reaction without solvent, though the yield is poor (Table IV.2, entry 5). After observing Table IV.2, we can conclude that EtOH is the superior for this novel purpose (Table IV.2, entry 3).



Scheme IV.5. Synthesis of Pyrazine derivatives from benzyl and ethylenediamine using onion extract.

Table IV.2. [a]Reaction conditions optimization by various solvents.

Entry	Solvent (5 mL)	Time (min.)	Yield(%)[b]
1	DMF	60	68
2	DCM	60	86
3	EtOH	60	96
4	H_2O	60	80
5	-	60	75
6	Hexane	60	55
7	DMSO	60	84
8	Isopropanol	60	76
9	Acetonitrile	60	69
10	Toluene	60	50

[a]Reaction of Benzil (1 mmol) and ethylenediamine (1 mmol) catalysed by onion extract (2 ml) on magnetic stirrer at room temperature. [b]Isolated yield of Pyrazine.

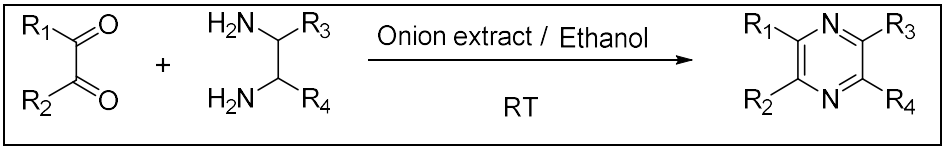
Next effort were undertaken to optimize the quantity of onion extract required to carry out the reaction. At first the substrates were stirred at room temperature for 120 minutes in the absence of onion extract, result rap out that onion extract play a key role to carry out the reaction (Table IV.3, entry 1), and also it was observed that minimum 0.2 mL onion extract and 60 minutes is sufficient enough to catalyze the reaction with better yield for desired product (Table IV.3, entry 6-10).

Table IV.3. [a]Reaction (Scheme-1) condition optimization.

Entry	Onion extract (mL)	Time(min.)	Yield (%)
1	0	120	Trace
2	1	120	97
3	0.8	120	97
4	0.6	120	97
5	0.4	120	96
6	0.2	120	96
7	0.1	120	95
8	0.2	90	96
9	0.2	60	96
10	0.2	45	92

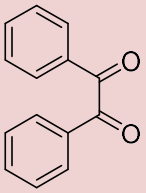
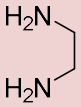
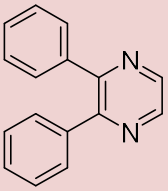
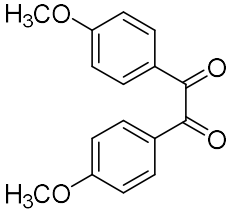
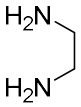
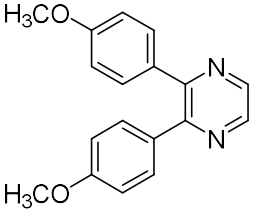
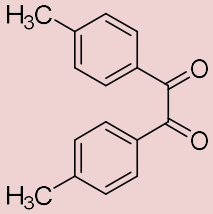
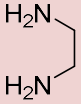
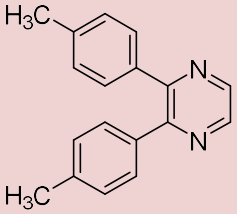
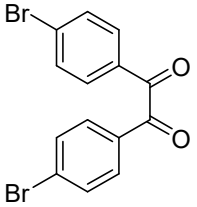
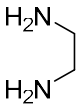
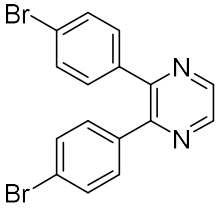
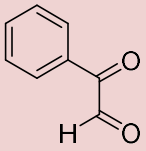
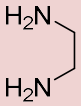
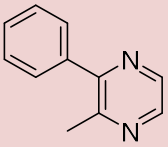
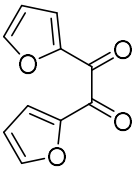
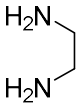
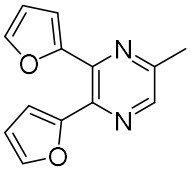
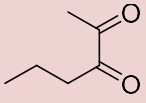
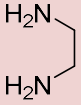
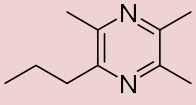
[a]Reaction of Benzil (1 mmol) and ethylenediamine (1 mmol) in EtOH (5 mL) on magnetic stirrer at room temperature.

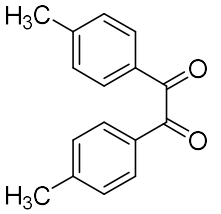
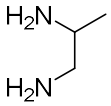
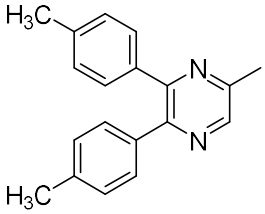
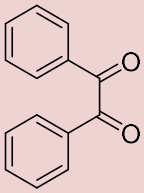
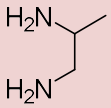
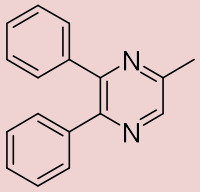
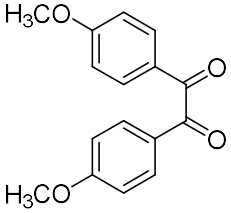
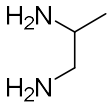
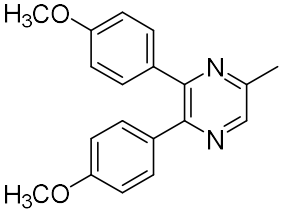
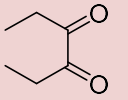
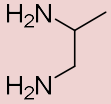
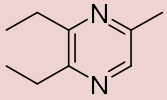
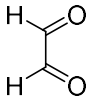
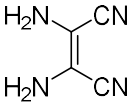
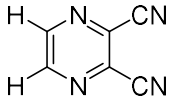
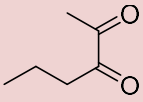
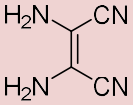
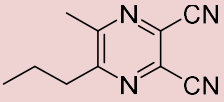
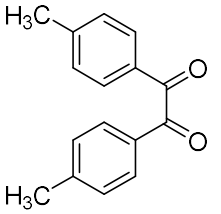
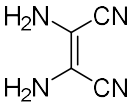
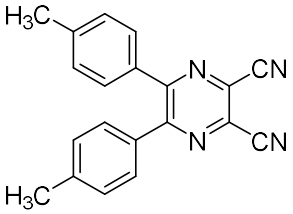
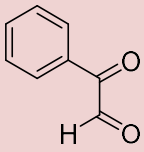
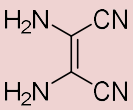
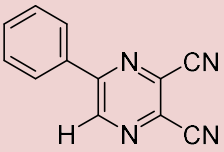
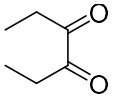
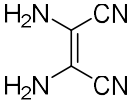
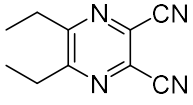
To widen the scope of our study, commercially available 1, 2-diketones and 1, 2-diamines are selected to synthesized corresponding products. As shown in Table 3, high yields were achieved for the synthesis of different Pyrazine derivatives within a reasonable time (Table IV.4, entry 1-15).

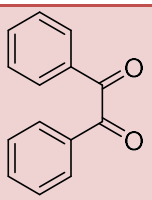
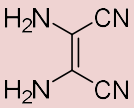
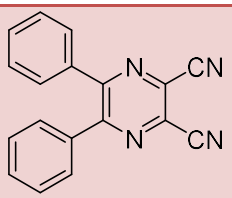


Scheme IV.6. The general scheme and reaction for the synthesis of Pyrazine derivatives using onion extract. R_1, R_2, R_3, R_4 are the different functional groups.

Table IV.4. Isolated yield and the catalytic synthesis of product.

Entry	Diketones	1,2-diamines	Product	Time (min)	Yield[b] (%)
1				60	96
2				70	94
3				80	96
4				50	92
5				45	89
6				60	89
7				50	90

8				50	94
9				90	96
10				70	95
11				70	93
12				60	89
13				45	85
14				50	87
15				80	89
16				70	86

17				45	88

[a]Reaction of Benzil (1 mmol) and ethylenediamine (1 mmol) in ethanol catalyzed by onion extract (0.2 ml) on magnetic stirrer. [b]Isolated yield of Pyeazine.

IV.8.B. Reusability of the catalyst and possible mechanism

The reusability study was examined for the onion extract catalyst (Figure IV.7). Our catalyst gave the desired product with good yield (96%-85%). The organic acids which are present in the onion extract were believed to serve as catalyst in the double condensation reaction and aromatization process to form Pyrazine derivatives.

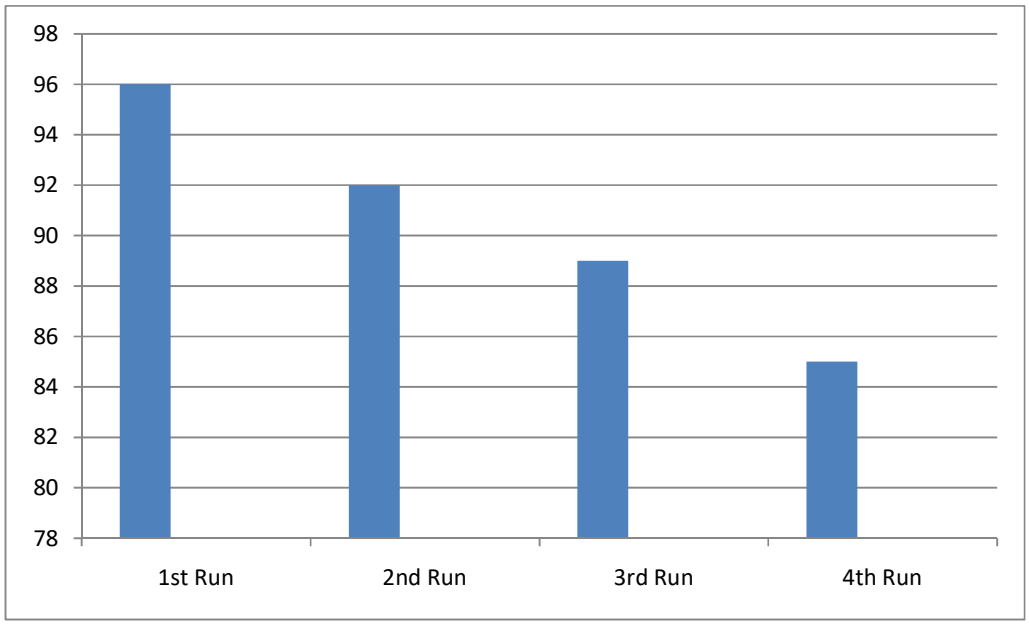


Figure IV.7. Reaction of Benzil (1 mmol) and ethylenediamine (1 mmol) in ethanol catalyzed by onion extract (0.2 ml) on magnetic stirrer. Recycling of our catalyst for synthesis of Pyrazine.

Literature report revealed that onion extract contain phenolic acids as major constituents along with other minor chemical constituents such as flavanols, flavones and anthocyanidines. The pH of the onion extract is found to be 3.6, which are due to the presence of water soluble phytochemicals- caffaeic acids, ferullic acid sinapinic acid, cyaniding, tannic acid and other organic acids. As they are water soluble that's

why we can easily collect the onion extract solution for our reusability purpose and we can also recover the acids after four successive usages. Therefore, we can propose the organic acids that are present in the onion extract served to protonate the oxygen atoms of the carbonyl groups of the diketone thereby faceiliting the nucleophilic attack by 1, 2-diamine promoting the synthesis of Pyrazine derivatives. From the above observation we can draw possible mechanism (**Figure IV.8**) and tentative intermediates in the synthesis of Pyrazine derivatives as follows.

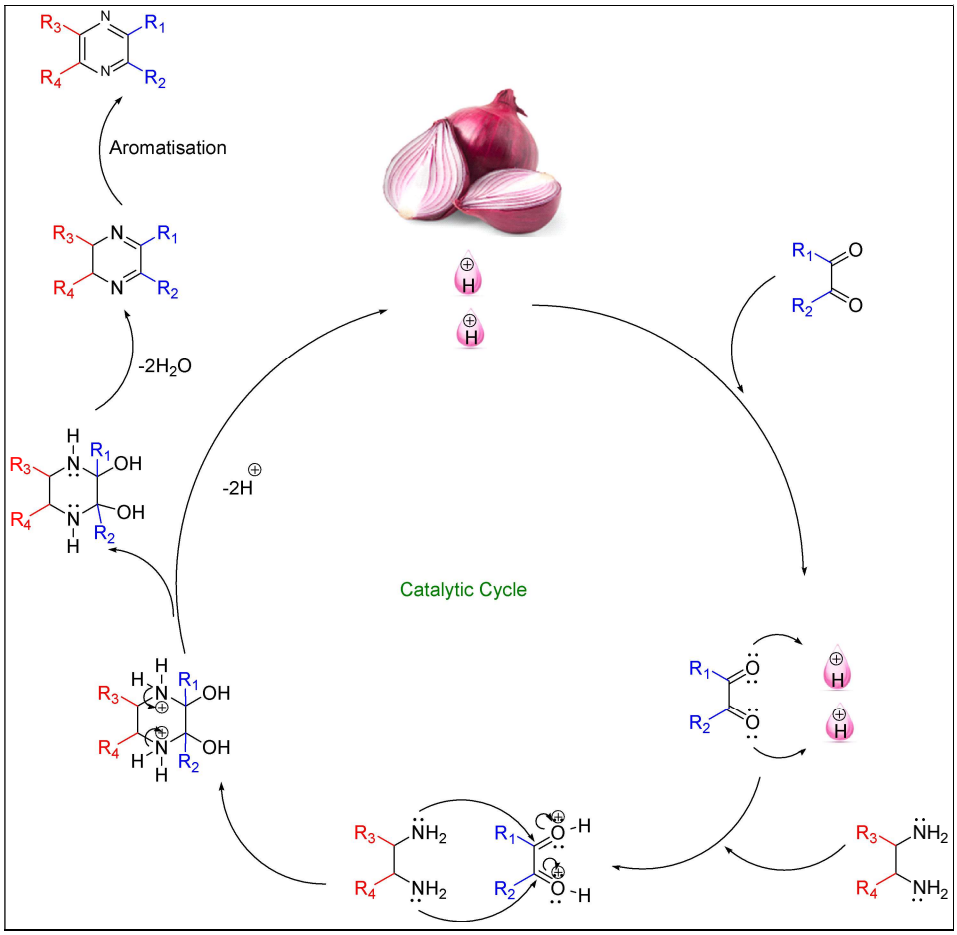


Figure IV.8. Possible mechanism and tentative intermediates in the synthesis of Pyrazine derivatives. R_1, R_2, R_3, R_4 are the different functional groups.

IV.8.C. Conclusion

In summary, we have achieved a simple and convenient procedure to synthesize Pyrazine derivatives in the presence of onion extract through condensation and aromatization from the easily available 1, 2-diketones and 1, 2- diamines. The current protocol offers many advantages including a simple and effective catalytic system, simple workup, benign reagents, cheap but good to excellent yields and the

reusability of the onion extract as a catalytic system. Further application of the onion extract in the synthesis of other bioactive heterocyclic compounds is currently ongoing in our laboratory and the results will be reported in due course.

IV.8.D. Experimental section

IV.8.D.i. General experimental detail

All the melting points were determined in an open capillary method; UV spectra were recorded in JASCO V-530 UV/VIS spectrophotometer; IR was recorded in Perkin-Elmer FT-IR spectrophotometer; and NMR was recorded in Bruker-Avance 300 MHz FT-NMR instrument using TMS as the internal standard. NMR spectra were recorded in $CDCl_3$. The entire chemicals were purchased from Merck, Fluka, SRL, and S.D. fine chemicals companies.

IV.8.D.ii. Preparation of Onion extract

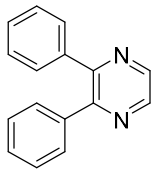
Onion was brought from local market and washed with water. Then squeezed the dry onion and filter it. The filtrate is onion extract and it is ready to use.

IV.8.D.iii. Representative Experimental Procedure for Reduction of Aromatic Nitro Compounds

In a round bottom flask Benzil (1 mmol), Ethylenediamine (1 mmol), Onion extract (0.2 mL) in 5 mL Ethanol at room temperature was stirred on a magnetic stirrer for 60 minutes. One cotton ball was present on the mouth of the round bottom flask during the process of reaction. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into 100 mL ice cold water and the product extracted with ethyl acetate, washed several times with water. Evaporation of solvent followed by column chromatography over basic alumina using petroleum ether/ethyl acetate (3:1) as eluent to afford the pure benzimidazole derivatives. The spectroscopic data (^{1}HNMR, ^{13}CNMR) of this compound are in good agreement with those reported.

IV. 8. E. Characterization of some representative compounds

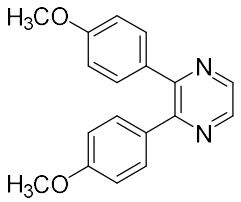
2, 3-diphenyl pyrazine



^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 7.14-7.25 (m, 5H, five aromatic hydrogen), 7.37-7.44 (m, 5H, five aromatic hydrogen), 8.52 (s, 2H, 2 aromatic hydrogen of the

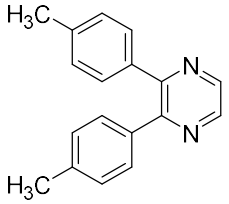
heterocyclic moiety). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 128.1, 128.2, 128.5, 129.5, 138.5, 141.9 and 152.6.

2, 3-bis (4-methoxy phenyl) pyrazine



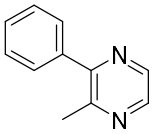
^1H NMR ($CDCl_3$, 300MHz): δ(ppm) 3.77 (s, 6H, 2-OCH3), 6.75-6.85 (m, 4H, four aromatic hydrogen), 7.33-7.43 (m, 4H, four aromatic hydrogen), 8.45 (s, 2H, two aromatic hydrogen of the heterocyclic moiety). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 55.2, 113.7, 130. 9, 131.2, 141.4, 152.1 and 159.9.

2, 3-di p-tolyl pyrazine



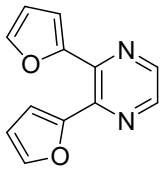
^1H NMR ($CDCl_3$, 300MHz): δ(ppm) 2.31 (s, 6H, 2-CH3); 7.04-7.12 (m, 3H, aromatic hydrogen), 7.27-7.46 (m, 5H, five aromatic hydrogen); 8.51 (s, 2H, two aromatic hydrogen of the heterocyclic moiety). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 21.3, 129.0, 129.4, 135.8, 138.5, 141.7 and 152.6.

2-methyl-3-phenyl pyrazine



^1H NMR ($CDCl_3$, 300MHz): δ(ppm) 2.54 (s, 3H, -CH3), 7.46-7.59 (m, 5H, five aromatic hydrogen), 8.44 (d, 2H, J=2.4Hz). 13C NMR (CDCl3, 75MHz): δ(ppm) 23.1, 128.4, 128.7, 128.9, 138.5, 141.5, 142.1, 151.8 and 154.4.

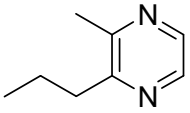
2, 3 di-(furan-2-yl)- pyrazine



^1H 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). ^{13}C NMR ($CDCl_3$,

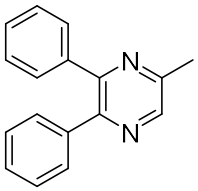
75MHz): δ(ppm) 21.3, 112.1, 112.7, 139.2, 140.8, 141.7, 143.4, 143.7, 150.5, 150.6, 151.2.

2-methyl-3-propylpyrazine



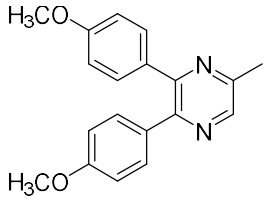
^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 0.96-1.04 (m, 3H, - CH3), 1.70-1.82 (m, 2H,), 2.57 (s, 3H, -CH3), 2.79 (t, 2H, J=7.5Hz). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 14.0, 21.5, 21.7, 36.9, 141.1, 141.4, 152.3, 156.0.

2, 3-diphenyl-5-methylpyrazine



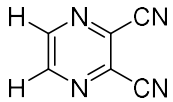
^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 1.86 (s, 3H, -CH3), 6.63 (d, 10H, J=5.1Hz, ten aromatic hydrogen), 7.68 (s, 1H, one aromatic hydrogen of the heterocyclic moiety). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 20.5, 127.4, 127.6, 128.7, 128.8, 137.8, 141.0, 148.8, 150.3, 150.7.

2, 3-bis (4-methoxy phenyl)-5-methylpyrazine



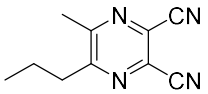
^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 2.62 (s, 3H, -CH_3), 3.80 (s, 6H, 2-OCH_3), 6.82 (dd, 4H, J=1.8 Hz, four aromatic hydrogen), 7.38 (dd, 4H, J=1.8 Hz, four aromatic hydrogen), 8.39 (s, 1H, one aromatic hydrogen of the heterocyclic moiety). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 21.2, 53.4, 55.2, 130.8, 130.9, 131.2, 131.4, 141.1, 149.0, 150.5, 150. 9, 159.8, 159.6.

Pyrazine-2, 3-dicarbonitrile



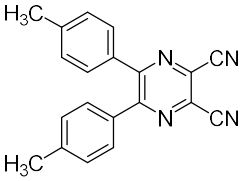
^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 9.00 (s, 2H, aromatic protons). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 113.1, 133.84 (aromatic carbons), 147.5 (-CN).

5-methyl-6-propiopyrazine-2, 3-dicarbonitrile



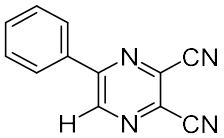
^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 1.06 (t, 3H, J=7.2Hz); 1.78-1.88 (m, 2H); 2.75 (s, 2H, -CH_3); 2.94 (t, 2H, J=7.5 Hz). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 13.8, 20.4, 22.3, 36.9, 113.3, 113.4, 129.9, 130.4, 157.7, 161.2.

5, 6-dip-tolylpyrazine-2, 3-dicarbonitrile



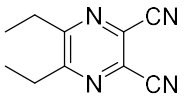
^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 2.32 (m, 6H, 2 -CH_3), 6.99 (m, 4H, aromatic protons), 7.43 (m, 1H, aromatic proton), 7.94 (m, 3H, aromatic protons). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 21.6, 126.8, 128.6, 129.3, 130.0, 139.2, 144.0, 144.3, 193.3.

5-phenylpyrazine 2, 3-dicarbonitrile



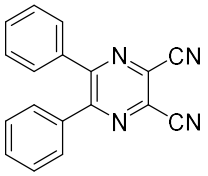
^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 7.61 (d, 3H, J7.5 Hz), 8.13 (d, 2H, J6.6Hz), 8.51 (s, 1H). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 128.0, 129.8, 130.8, 132.5, 133.0, 144.1, 154.8.

5, 6-diethylpyrazine-2, 3-dicarbonitrile



^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 1.39 (m, 6H), 1.97(m, 2H), 2.97 (m, 2H), ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 11.2, 19.8 (2-CH3); 25.1, 27.8 (2-CH2); 113.4, 130.2 (aromatic carbon); 161.3 (-CN).

5, 6-diphenyl pyrazine-2, 3-dicarbonitrile



^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 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). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 126.5, 127.5, 128.2, 128.4, 130.0, 132.4, 137.5, 143.8, 196.8 (carbon of nitrile group).

IV.8.F. Scane copy of 1H NMR, 13 C NMR ofsome pyrazine derivatives

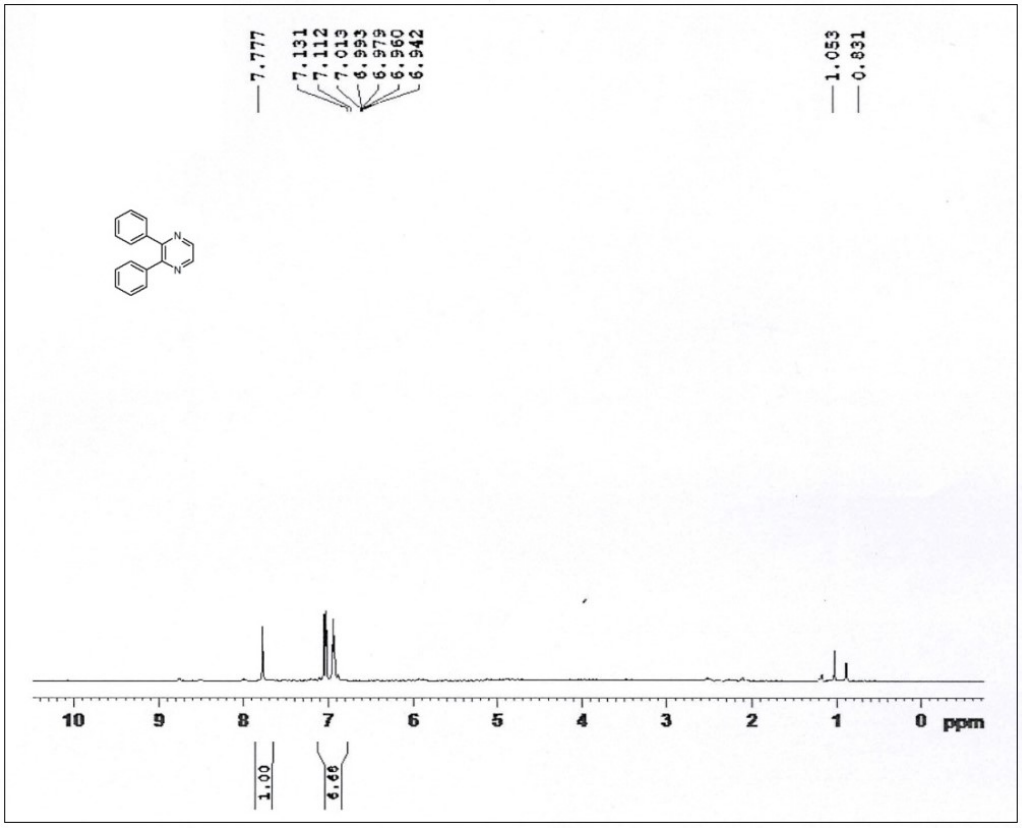


Figure IV.9. ^{1}HNMR of 2,3-diphenylpyrazine.

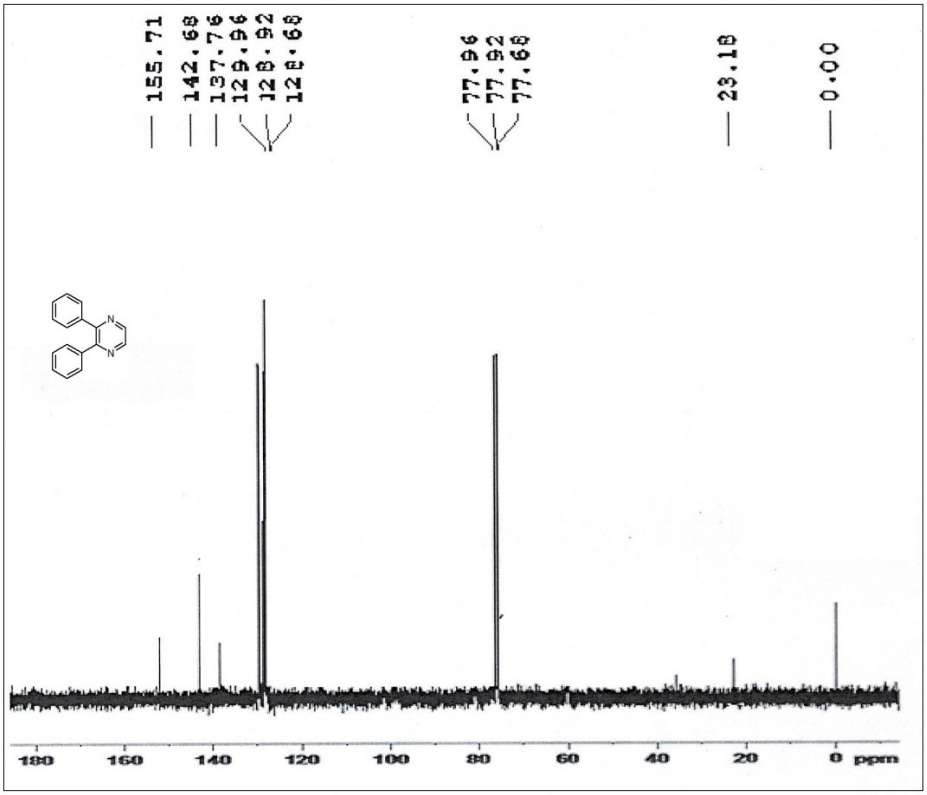


Figure IV.10. ^{13}C NMR of 2,3-diphenylpyrazine.

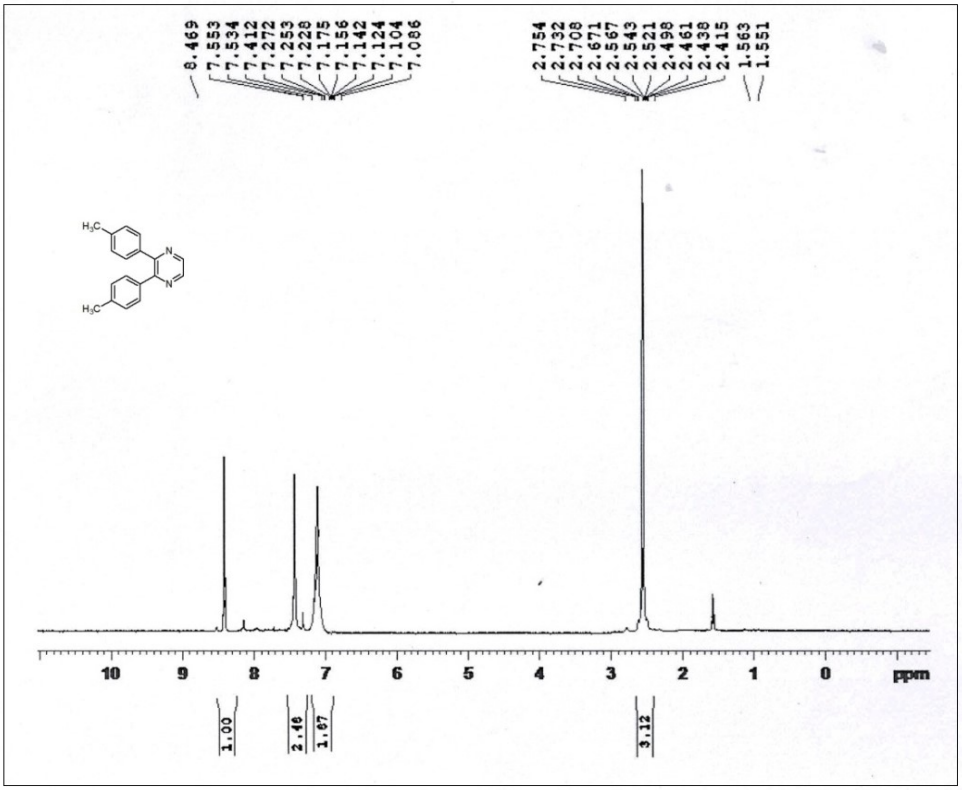


Figure IV.11. ^{1}HNMR of 2, 3-di p-tolyl pyrazine.

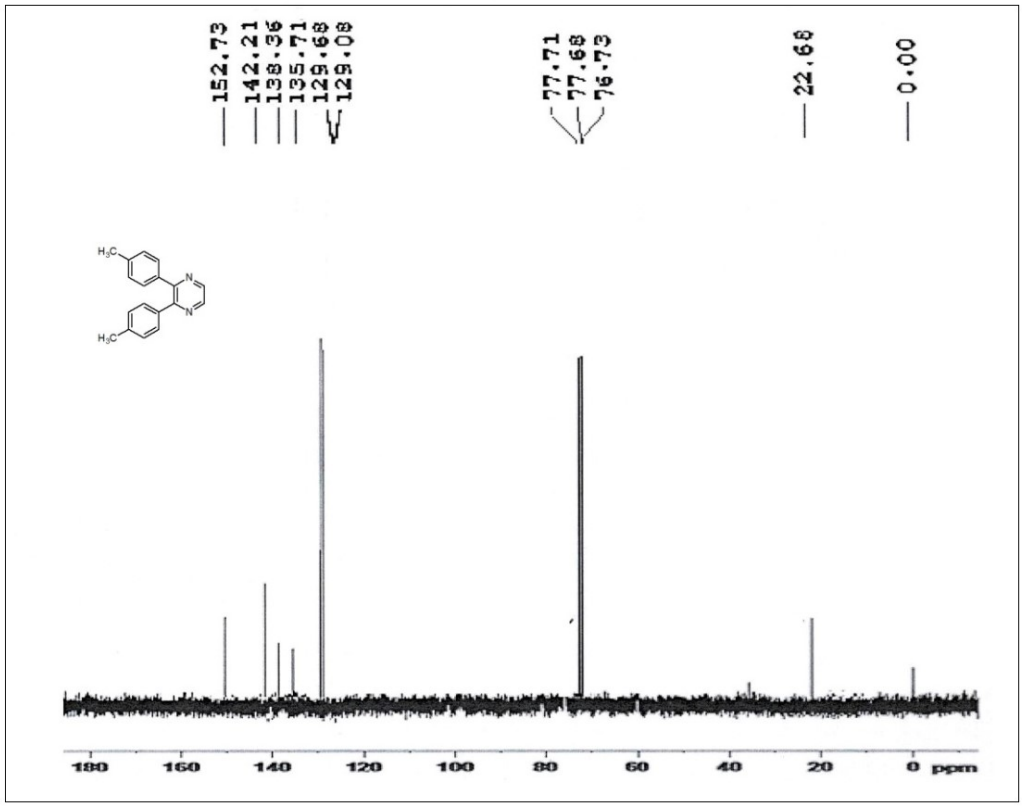


Figure IV.12. ^{13}C NMR of 2, 3-di p-tolyl pyrazine.

I.G. References

References are given in BIBLIOGRAPHY under Chapter IV.