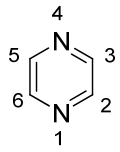
CHAPTER 1: SYNTHESES AND REACTIONS OF PYRAZINE AND QUINOXALINE

1.1 Pyrazine

Pyrazine **(1)** is an aromatic six-membered heterocycle that contain two nitrogen atoms. It also known as 1,4-diazine. This heterocycle can be regarded as aromatic in character and their chemistry has very little in common with benzene although their resonance energy is lower than benzene. The numbering system universally used for pyrazine is as shown.



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Pyrazine is stable, colourless compound and its dipole moment is zero. The boiling point of pyrazine is 116°C and the melting point is 54°C. Most of the lower homologs 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 shown that the ring is planar and the carbon-carbon distance is longer than benzene which is 1.40Å.

Pyrazine represent an important class of heterocyclic compounds.[1-4] This structural unit is found in many natural products. They are important flavour ingredient in food[5,6] which occur as flavour constituents of peas, coffee, Capsicum peppers and wines.[7] Although present in very small amounts, they are extremely odorous and can be detected at concentration as low as 0.00001 ppm. Pyrazines have also shown interesting anticancer[8-11] as well as antituberculosis[12-16] activities.

1.1.1 Pyrazine and reactivity

Since pyrazine is an aromatic heterocycles, therefore it should undergo electrophilic aromatic substitution. The resonance hybrid of pyrazine is as shown in Figure 1.1.

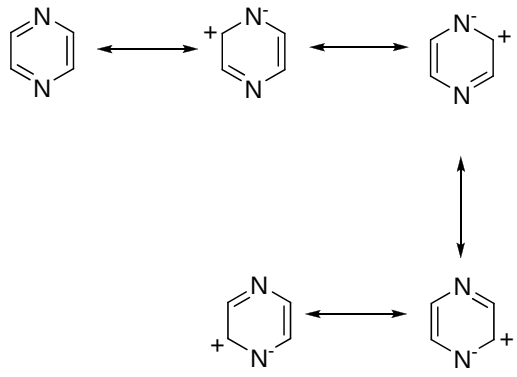
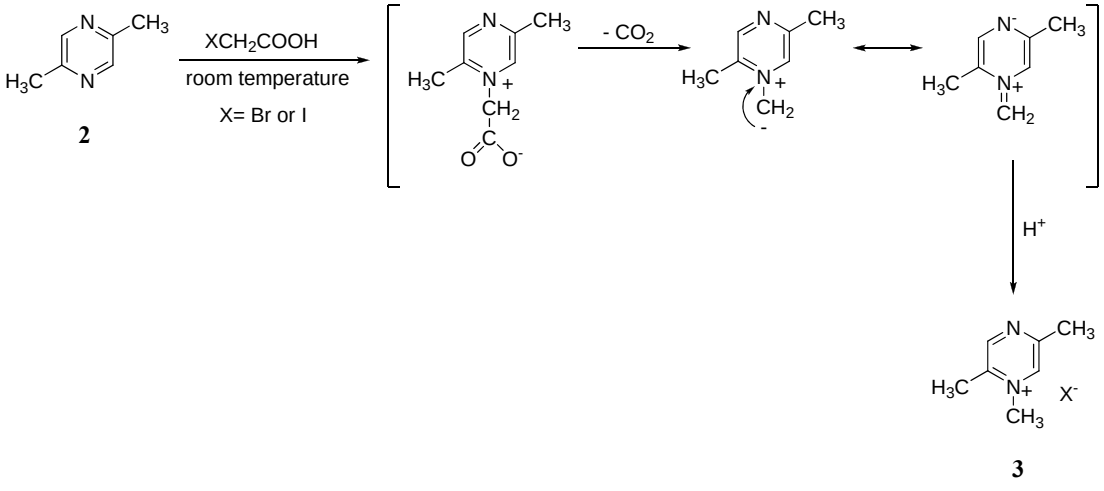


Figure 1.1: Resonance hybrid of pyrazine

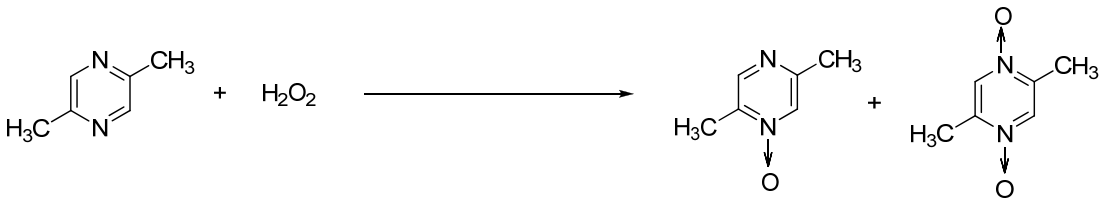
From the canonical forms shown in Figure 1.1, it can be seen that the electron deficiencies are at 2, 3, 5 and 6 positions. Therefore, nucleophilic reagents could attack at the 2, 3, 5 and 6 positions. However, studies have shown that the nucleophiles attacked the ring only if there is at least one powerful electron releasing group such as NH_2, OH, SH in another position. The presence of two nitrogen atoms in the ring influence on both the basicity and the aromatic properties of the pyrazines.

Pyrazine is a tertiary amine, and is a weaker base than pyridine.[17] In general, pyrazine behaves as monoacidic bases[18] and form diacidic salts under anhydrous conditions. Pyrazine forms monoquaternary salts[19,20] with alkyl halides which are unstable and are best prepared at temperature below 40°C. Pyrazine also reacts with halogenated acids to form pyrazinium salt as shown in Scheme 1.1, whereby 2,5-dimethylpyrazine **(2)** reacts with iodo or bromo-acetic acid to give 1,2,5-trimethylpyrazinium salt **(3)**, as demonstrated in Scheme 1-1 below.[21]



Scheme 1.1: Reaction of 2,5-dimethylpyrazine with iodo or bromo-acetic acid

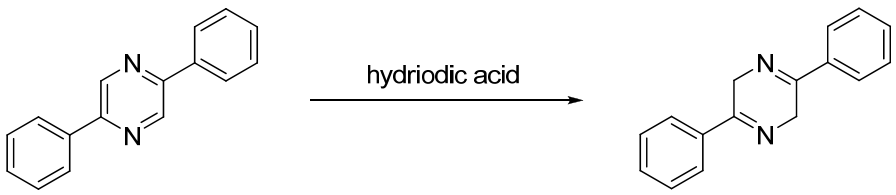
Pyrazine undergoes oxidation process, whereby it decolarises cold alkaline solution of permanganate[22] but pyrazine is less stable than pyridine to the action of oxidizing agents. Mono **(4)** and di-N-oxides **(5)**[23] were obtained when alkyl pyrazine react with hydrogen peroxide as shown in Scheme 1.2.



2 **4** **5**

Scheme 1.2: Reaction of alkyl pyrazine with hydrogen peroxide

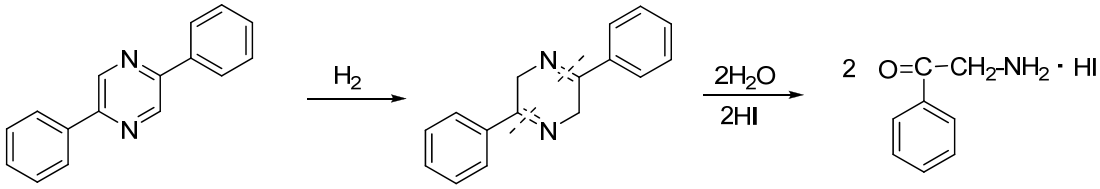
Pyrazines are readily reduced to saturated piperazines by sodium and alcohol[24-26], aluminium amalgam, sodium amalgam, tin and hydrochloric acid.[27] For example, 2,5-diphenyl-3,6-dihydropyrazine **(7)** was obtained when 2,5-diphenylpyrazine **(6)** was treated with hydriodic acid and red phosphorus, as shown in Scheme 1.3.



6 **7**

Scheme 1.3: Reaction of 2,5-diphenylpyrazine with hydriodic acid

In general, pyrazines are stable to alkali and acids, however experiments with certain aryl derivatives show that hydriodic acid can cleave the nucleus of the pyrazine ring.[28] It is believed that this reagent first reduces the pyrazine to a dihydro derivative which is readily hydrolyzed as shown in Scheme 1.4. The mechanism of the reaction have not been investigated, but the transformation of 2,5-diphenylpyrazine **(6)** to aminoacetophenone **(8)** would be possible.



6 **8**

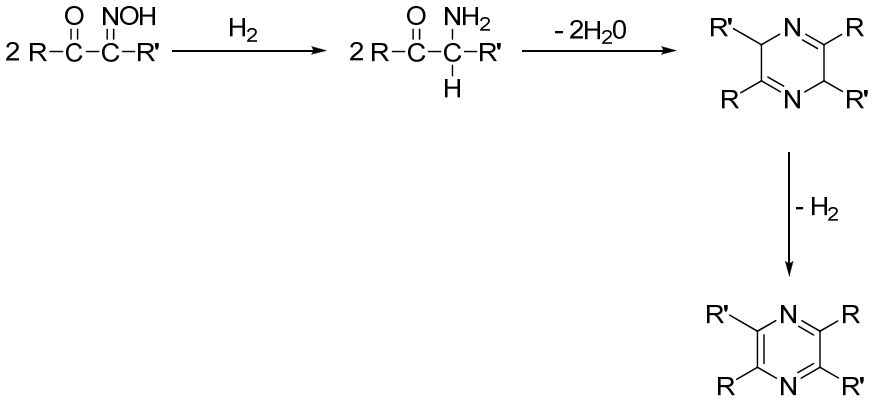
Scheme 1.4: Transformation of 2,5-diphenylpyrazine to aminoacetophenone

1.1.2 Synthesis of pyrazine derivatives

1.1.2.1 Reduction of nitrosated ketones

The synthesis of pyrazine was first recorded by Laurent[29] in 1844. Laurent's method was vague, however, more than fifty years later, the compound was proved to be tetraphenylpyrazine[30]. The systematic study of pyrazine series of compounds was initiated by Gutknecht[31] and Treadwell[32] who discovered that the reduction of nitrosated ketones resulted in the formation of oxygen free bases instead of the expected α-amino ketones.

The transformation of this reaction is represented in Scheme 1.5.

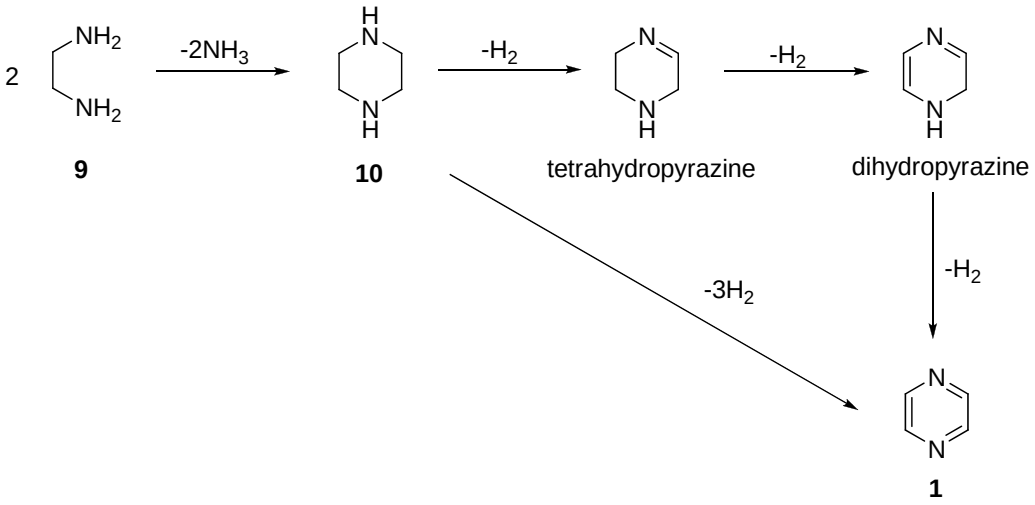


Scheme 1.5: **Reduction of nitrosated ketones**

Gabriel and Pinkus[33] further extended the field of synthesis by adding the oxidising agents to the reaction mixture after the condensation had been allowed to take place. As a result, higher yields were obtained. Gabriel demonstrated the intermediate formation of dihydropyrazines by the isolation of these compounds under anaerobic conditions and subsequent oxidation to the corresponding pyrazines. The correct structure of pyrazine was discovered by Wleugel[34] in 1882.

1.1.2.2 Intermolecular deamination and cyclisation of ethylenediamine

Many researchers studied the deamination reactions using various catalysts, but not on the deamination reaction leading to the cyclisation process. B. Madhavi Latha et al.[35] has reported the deaminocyclisation of ethylenediamine **(9)** followed by dehydrogenation over copper chromite catalysts resulted in the formation of pyrazine **(1)** with greater selectivity. A general reaction pathway for the synthesis of pyrazine using this method is shown in Scheme 1.6.



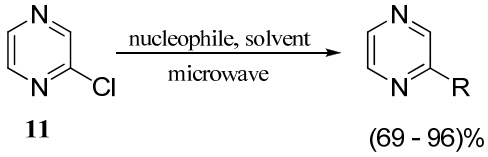
Scheme 1.6: Intermolecular deamination and cyclisation of ethylenediamine

In this method, ethylenediamine vapour was passed over a series of copper oxide/copper chromite catalysts in the temperature range of 340°C - 440°C. Two molecules of ethylenediamine condensed to form piperazine **(10)** by releasing two molecules of ammonia, which further dehydrogenated to form pyrazine as a major product. The formation of pyrazine as the major component suggests the high activity of the copper based catalysts to effect spontaneous dehydrogenation of piperazine.[36]

1.1.2.3 Microwave irradiation

The application of microwaves in promoting organic reactions has received intense attention recently.[37,38] Under microwave irradiation, Y.J. Cheng[39] has developed an ancillary method for acceleration of nucleophilic aromatic substitution reactions.

In this method, the formation of substituted pyrazines were obtained by the interaction of 2-chloropyrazine **(11)** with the nucleophiles of PhSNa, MeSNa, EtONa and PhONa in *N*-methylpyrrolidone (NMP) which gave the desired substitution products in a good yield of (69 – 96)%.[40] The reactions of 2-chloropyrazine **(11)** with nucleophiles as shown in Scheme 1.7.



11 (69 - 96)%

Scheme 1.7: Formation of substituted pyrazines

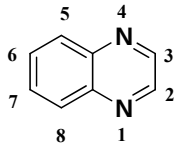
Table 1.1: Interaction of 2-chloropyrazine with nucleophiles

Entry	Nucleophile	Solvent	Molar proportions of nucleophiles	Temperature (°C)	Time (s)	Product, R=	Yield (%)
1	PhSNa	NMP	2	80	35	SPh	96
2	MeSNa	NMP	1.7	80	50	SMe	88
3	EtONa	NMP	1.8	90	45	OEt	68
4	PhONa	NMP	2	100	50	OPh	69

Data taken from reference 40

1.2 Quinoxaline

Quinoxaline **(12)** is also known as benzopyrazine. The name comes from the fusing of benzene to a pyrazine ring. Quinoxaline melts at 31°C and boils at 223°C. The numbering of the carbon in the quinoxaline system is as shown in **(12)**.



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In general, the physical properties of the quinoxalines are quite similar to those of the pyrazines. The parent compound is miscible with water in all proportions. The quinoxalines can form hydrates readily. The hydrates have greater stability at lower temperatures. Because of that, some derivatives are more soluble in cold water than in hot water.

Quinoxalines are very important compounds due to their wide spectrum of biological activities behaving as anticancer[41], antiviral[42], antibacterial[43], and activity as kinase inhibitors.[44] Although rarely described in nature, synthetic quinoxaline ring is a part of a number of antibiotics such as echinomycin, leromycin, and actinomycin, which are known to inhibit the growth of Gram-positive becteria and are also active against various transplantable tumors.[45,46] In addition to medicinal applications, quinoxaline derivatives have been used as dyes[47], efficient electroluminescent materials[48], DNA cleaving agents[49,50] and building blocks in the synthesis of organic semiconductors.[51]

Due to its significant applications in the fields of medicinal, industrial and synthetic organic chemistry, there has been tremendous interest in developing efficient methods for the synthesis of quinoxalines. Consequently, various methods have been developed for the synthesis of quinoxaline derivatives. This will be discussed later in the chapter.

1.2.1 Quinoxaline and reactivity

Quinoxaline can be considered as a resonance hybrids as shown in Figure 1.2.

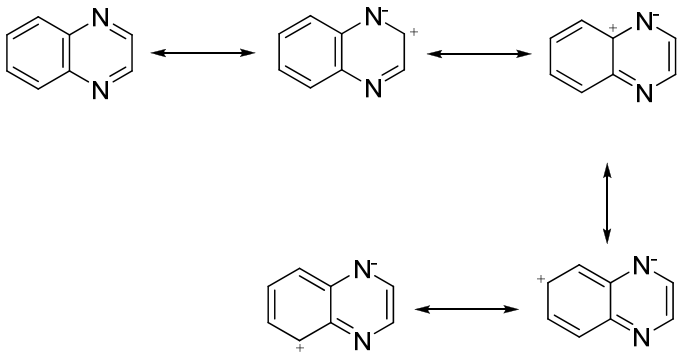


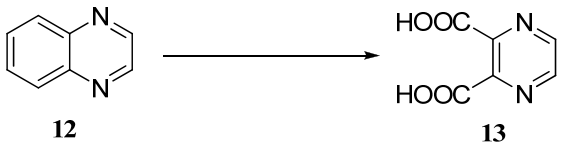
Figure 1.2: Resonance hybrids of quinoxaline

Many of the reactions of quinoxalines can be explained by a consideration of the charged canonical forms of the N-heterocyclic ring systems in a similar way to that of pyrazine as explained in Section 1.1.1. However, in the case of quinoxalines, the effect of the benzene ring that fused to the pyrazine need to be considered.

In analogy with Pauling's concept of the relationship between naphthalene and benzene, Krems and Spoerri[52] have pointed out that the carbon to nitrogen bonds involving carbon atoms 2 and 3 of quinoxaline would be expected to display a higher degree of unsaturation than the corresponding bonds in pyrazine. This viewpoint serves as a possible explanation of the fact that nucleophilic reagents in general appear to add more readily to quinoxaline than pyrazine.

Quinoxaline is also very weak base.[53] The parent compound and its alkyl and aryl derivatives yield only monoacidic salts under ordinary conditions.[54] Although the quinoxaline may be converted to monoquaternary salts with alkyl halides, the reaction often takes place slowly, the salts are unstable and the yields are low.[55-58] Therefore, the quaternisation usually best accomplished by prolonged reactions at low temperatures.

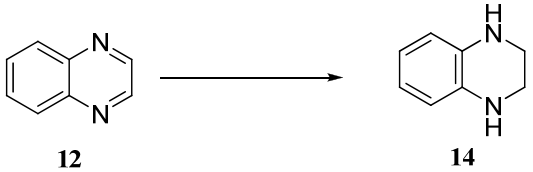
It has been reported that the quinoxaline nucleus is inert to the oxidizing action of nitric acid and of potassium dichromate[59], but it is readily attacked by alkaline permanganate yielding pyrazine-2,3-dicarboxylic acid **(13)** as shown in Scheme 1.8. The conversion of quinoxaline **(12)** to pyrazine-2,3-dicarboxylic acid **(13)** takes place smoothly and in good yield.[60,61] This conversion also showed that pyrazine ring is more stable than the benzene ring.



12 **13**

Scheme 1.8: Conversion of quinoxaline to pyrazine-2,3-dicarboxylic acid

The quinoxalines are easily reduced to dihydro compounds but it is difficult to be isolated. Complete reduction of quinoxaline **(12)** to 1,2,3,4-tetrahydroquinoxaline **(14)** is accomplished with sodium and alcohol[62-65] as shown in Scheme 1.9.



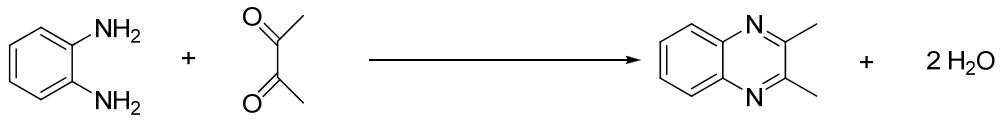
12 **14**

Scheme 1.9: Reduction of quinoxaline to dihydro compound

1.2.2 Synthesis of quinoxaline derivatives

1.2.2.1 Condensation reaction

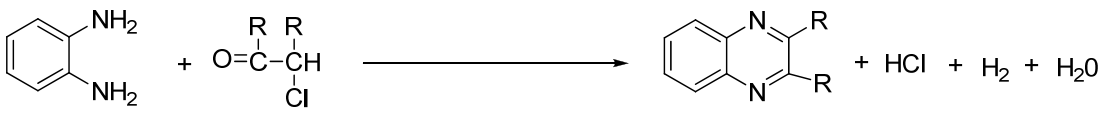
The classical synthesis of quinoxalines involves the condensation of an aromatic 1,2-diamine **(15)** with a 1,2-dicarbonyl **(16)** compound as shown in Scheme 1.10. This reaction was discovered many years ago by Korner[66] and by Hinsberg[59] independently. The reaction is facile and it is the most frequently used method for synthesizing both quinoxaline and its derivatives.[67]



15 **16**

Scheme 1.10: Condensation of 1,2-diamine with 1,2-dicarbonyl compound

The second early method for the preparation of quinoxalines involves α-haloketones whereby α-haloketones were condensed with aromatic *o*-diamines[68,69] as shown in Scheme 1.11. The dihydroquinoxaline, which is the primary condensation product, is readily oxidised to the corresponding quinoxaline which is not isolated under the standard conditions. Since this type of synthesis is much less satisfactory than that in which diketones are employed, it is of only academic interest.



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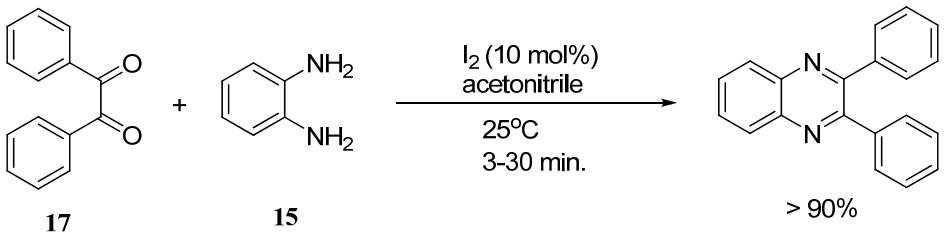
Scheme 1.11: Condensation of α-haloketones with *o*-diamines

1.2.2.2 Catalysts as precursors

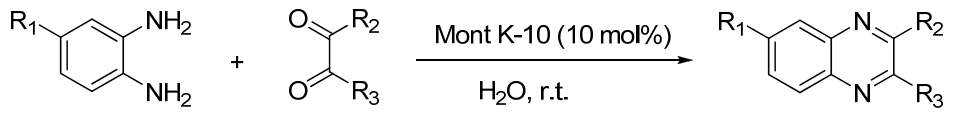
Quinoxaline has also been obtained by using catalysts as precursors. There are a few methods to synthesise quinoxaline derivatives using this method. One of the methods reported is by using molecular iodine as the catalysts. S. V. More et al.[70] had reported that the reaction of 1,2-diketone **(17)** and 1,2-diamine **(15)** which subjected to condensation using catalytic amount of iodine affords the quinoxalines in excellent yields as shown in Scheme 1.12.



Scheme 1.12: Preparation of quinoxaline derivatives through iodine catalysis

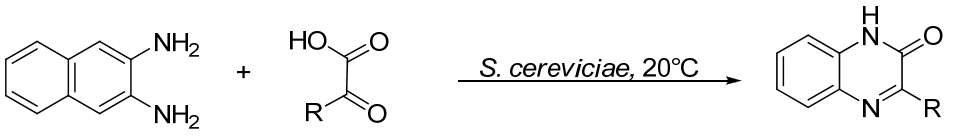
Although the role of iodine is not clearly known, it can act as a mild Lewis acid. Apart from its acidity, iodine plays a complex role in accelerating the dehydrative steps, and thus promotes the formation of products.[71] This procedure makes it significant as an alternative platform of environmentally greener and safer processes which employed an easy workup procedure with high reaction rates and excellent product yields.

Besides molecular iodine, the condensation of 1,2-diamine with 1,2-dicarbonyl compounds catalyzed by Montmorillonite K-10 (Mont K-10) in water can also produced high percentage yield of product. This reaction was carried out by T. –k. Huang et al.[72] and as shown in Scheme 1.13. Most of the reactions proceed very cleanly at room temperature and no desirable side-reactions were observed.



Scheme 1.13: Preparation of quinoxaline derivatives through Mont K-10 catalysis

J. Gris et al.[73] had synthesized several quinoxalinone derivatives by reacting 2,3-diaminenaphthalene with a variety of α-ketoacids through enzymatic catalysis as shown in Scheme 1.14. The products were obtained by mixing the starting materials and *Saccharomyces cereviciae* in a sucrose solution. More than 90% of the product was obtained.



R= -CH_3 (a), -C_2H_5 (b), -$(CH_2)_2$-CO_2H (c), -CH_2-CO_2H (d), -CH_2-C_6H_5, e) -OH (f)

Scheme 1.14: Preparation of quinoxalinone through enzymatic catalysis

1.3 Objectives of study

The aim of this project is to synthesis derivatives of pyrazine and quinoxaline, started with halogenated starting material with various amines and phenols to form *N*-alkylamino, *N*-arylamino, and phenoxy derivatives respectively. Various synthetic methods were investigated in order to obtain high percentage yield of the products. The second part of the project is to investigate the fluorescence characteristics of all the compounds prepared.

Fluorescence works were carried out using Fluorescence Spectrophotometer and the studies were based on:

i. Influence of solvents

ii. Influence of pH

iii. Influence of substituents

iv. Influence of concentrations

v. The ring systems

vi. Quenching by oxygen or air