CHAPTER- Ⅰ

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

CHAPTER- Ⅰ

SECTION-A

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

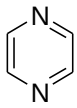
Ⅰ. A.1. Pyrazine

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

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

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

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



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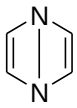

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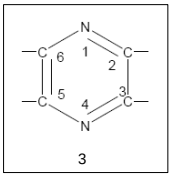
The nomenclature of pyrazines was even difficult because of the fact that early workers were in confusion regarding the structure of pyrazine. 2, 5-dimethylpyrazine was thought to be the parent compound of the class and was given the generic name“ ketine.”Following the ring index, [8] the numbering of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



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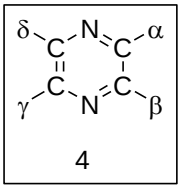
An alternative scheme was used by T.Tictor and V. Richter in his *Lehrbuch der organischen Chemie*



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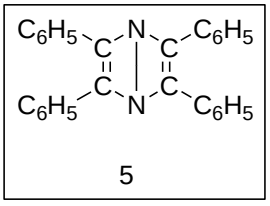
Historically the structure elucidation of pyrazine derivative was first made by japp and Wilson and later by Pauling Japp and Wilson[9]. They started determining the true nature of benzoinimide and renamed it as ditolanazotide. Finally Japp and Burton [10] decided that the compound was azine and assigned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



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

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

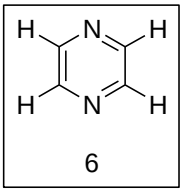

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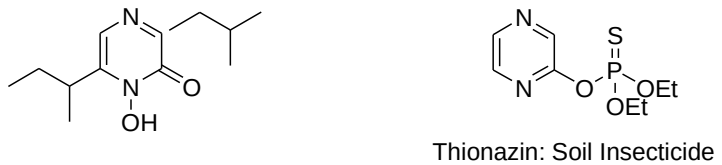
Figure. Ⅰ.A.6. Finally accepted structure of pyrazine

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



Aspergillic acid: Fungal Antibiotics

Thionazin: Soil Insecticide

7

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

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

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

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

Ⅰ.A.2. Natural Occurance

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

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

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

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

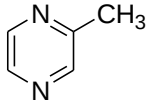
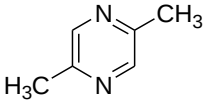
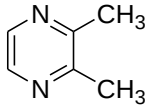
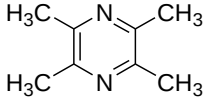
Pyrazines	Source	References
2,5-Dimethylpyrazine 2,3,5Trimethylpyrazine 2,5-Diethylpyrazine	Fusel Oil	Cheesman, 1972
Alkylpyrazines	Commercial peanut butter preparation	Joo et al, 1997
2,3-Dimethylpyrazine 2-methylpyrazine 2,3,5Trimethylpyrazine	Chitin pyrolysis at 300-500^{0}C	Knorr et al, 2006

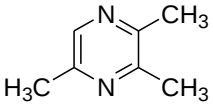
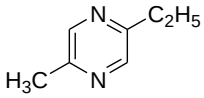
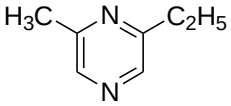
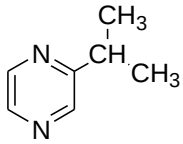
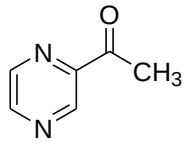
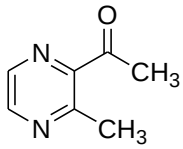
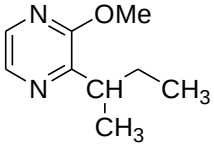
Table. Ⅰ.A. 2. Occurance of pyrazines in animals

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

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

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

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

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

Ⅰ.A.3. Structure of pyrazine

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

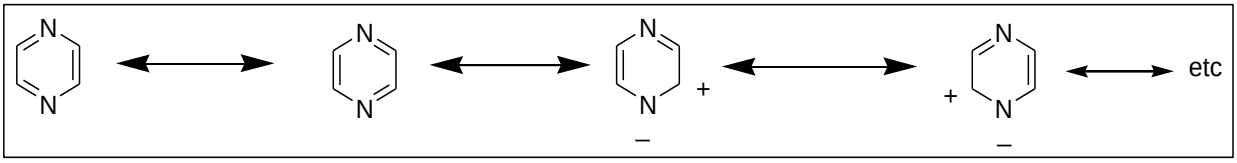


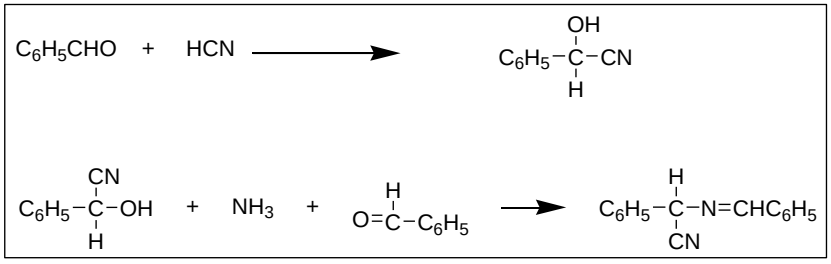
Fig. Ⅰ.A.8. Resonance structures of pyrazine

Ⅰ.A.4. Application of pyrazines

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

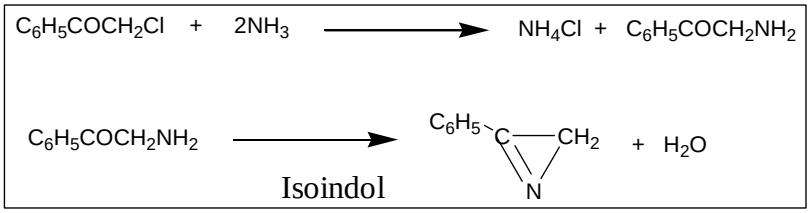
Ⅰ.A.5. Method for the synthesis of pyrazine

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



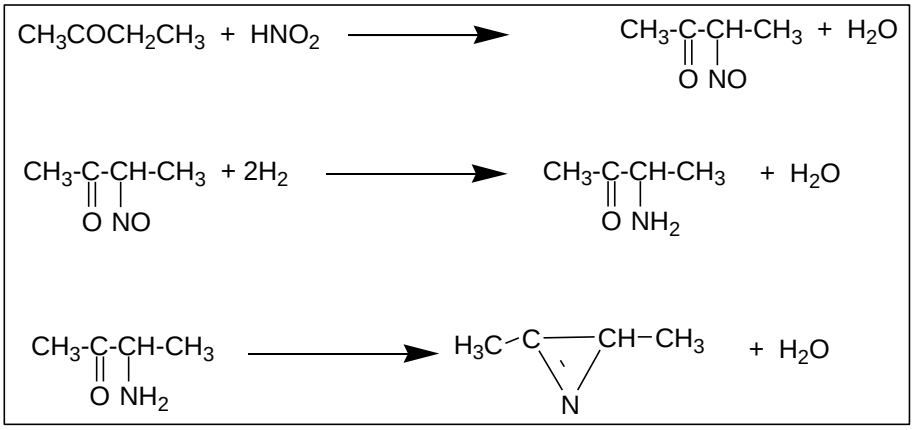
Scheme. Ⅰ.A. 1. Synthesis of α-benzalaminophenylacetonitrile

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



Scheme. Ⅰ .A. 2. Synthesis of isoindol

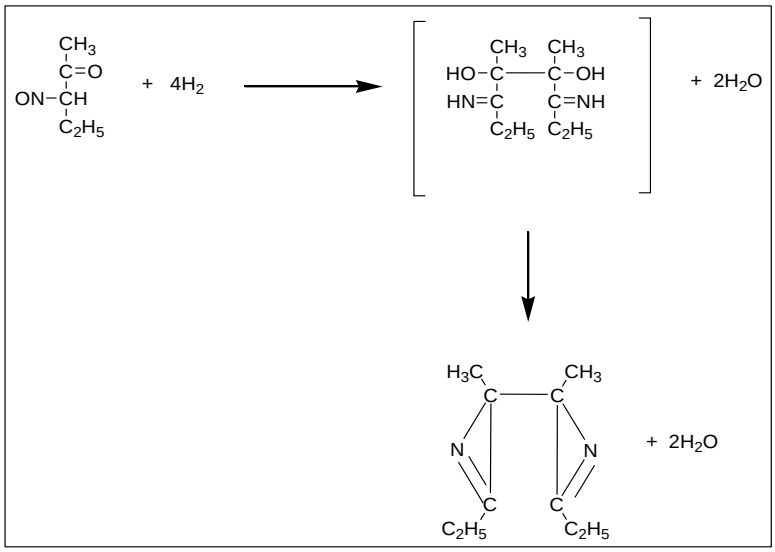
This compound represented the first inatance of a structural formula for pyrazine. In 1881, Etard[22] obseved a new compound, glycolin, that could be isolated from the distillate, resulted from heating a mixture of ammonium salt and glycerol. But Victor Meyer already elucidated the nature of this compound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



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

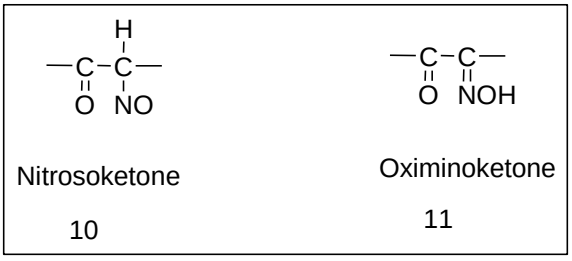
After a lot of analysis, Gutknecht thought that the compound might contain one hydrogen atom less that was indicated by the formula. Finally F. P. Treadwell.[23] clarified the point in 1881. He reduced" nitrosoethylacetone" and isolated a crystalline hydrate. After keeping the crystal in desiccators,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

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

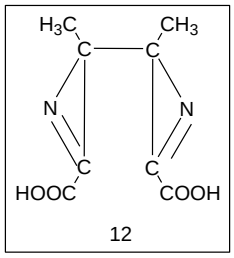


Scheme. Ⅰ.A. 4. Synthesis of nitrosoethylacetone

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



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



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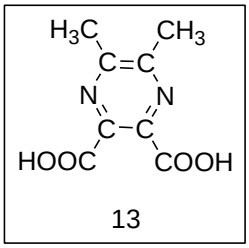
Utilizing the C-C bonds involved in the inner anhydride ring, he closed the six-membered ring as follows:



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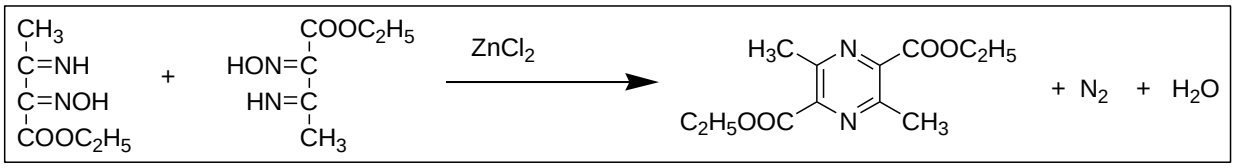
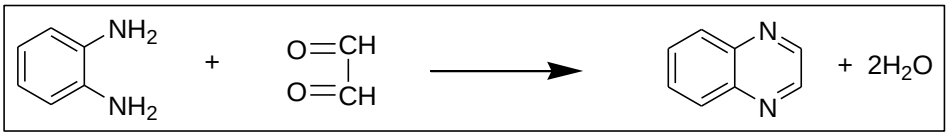
This led to the formulation of a heterocycle, which according to Wleugel, conceived to be pyridine, where CH group para to nitrogen was replaced by another nitrogen atom. This is the modern concept of pyrazine nucleus. But there remained a defect in derivation, since Wleugel had utilized the ketine (pinacol)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



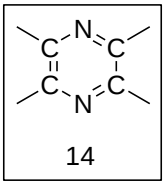
Scheme. Ⅰ.A. 5 . Oeconomides's Synthesis of pyrazine derivative

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



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

Thus, the structure of ketine nucleus was established as



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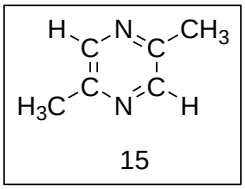
And ketine, that was thought to be simplest member, infact was dimethyl derivative.



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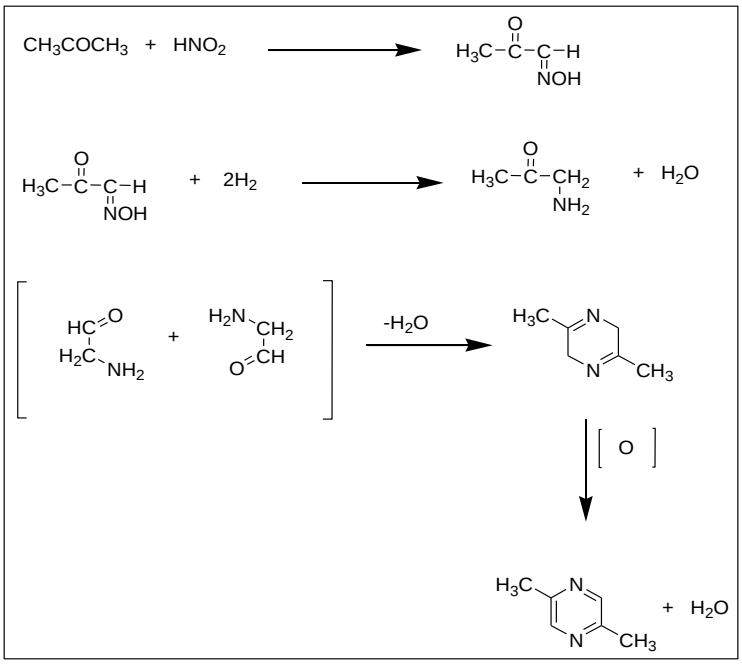
Mason [28] and Wolff [29] independently suggested the name pyrazine in order to correlate with pyridine. Wolff acknowledged that the mechanism put forth by Meyer , that gave rise to pyrazine by reduction of isonitroso ketone had an intermediate amino ketone which condensed with it immediately to yield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



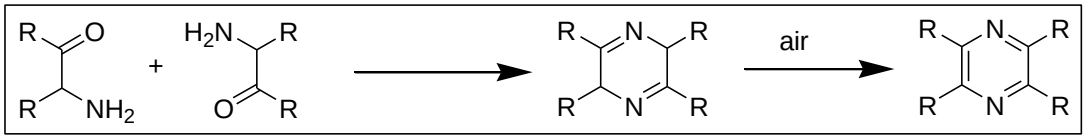
Scheme. Ⅰ.A. 7. Mason's synthesis of pyrazine

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

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

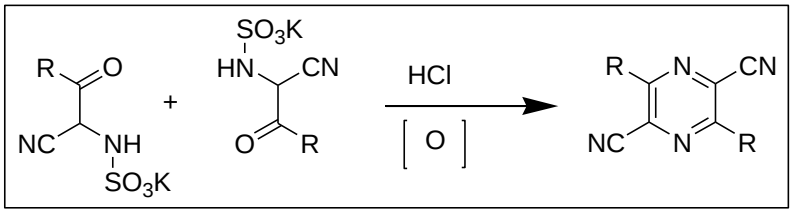
Historically simple pyrazine was synthesized as early as in 1876 by Stacdel-Rugheimer.[33] In this method, 2-chloroacetophenone was reacted with ammonia to form amino ketone, this got condensed and oxidized to pyrazine. In 1879 Gutknecth modified the method a little. This method was also self-

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



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

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



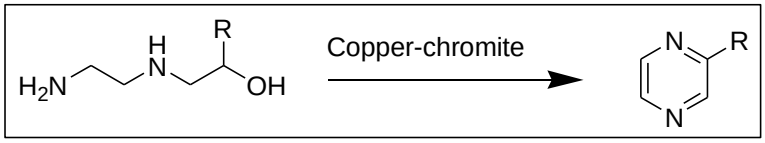
Scheme. Ⅰ.A. 9. Gastaldi's method for synthesis of pyrazine

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

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

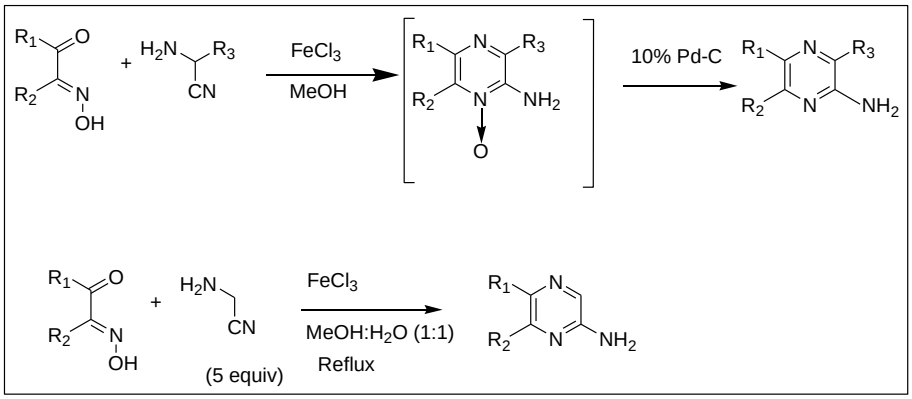
Scheme. Ⅰ.A.10.Reaction of 2, 3-diamino-3-phenylthioacrylonitrile with 2, 2-diethoxyacetophenone.

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



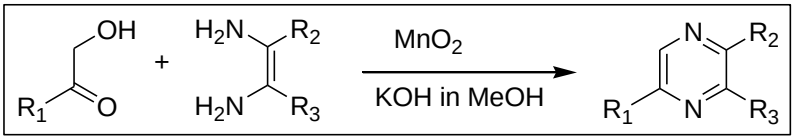
Scheme. Ⅰ.A. 11. Synthesis of pyrazine by copper chromite

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



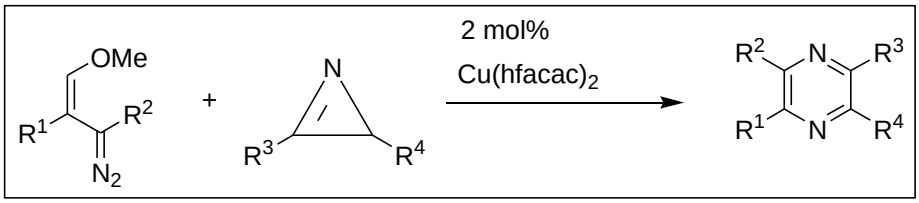
Scheme. Ⅰ.A. 12. Synthesis of pyrazine by $FeCl_3$

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



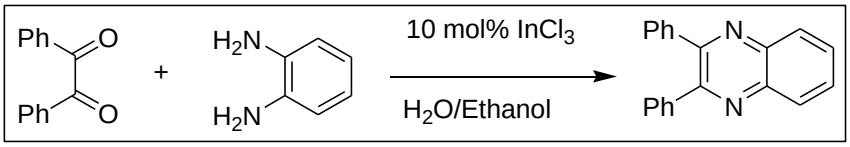
Scheme. Ⅰ.A. 13. Catalytic formation of pyrazine by Richard

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



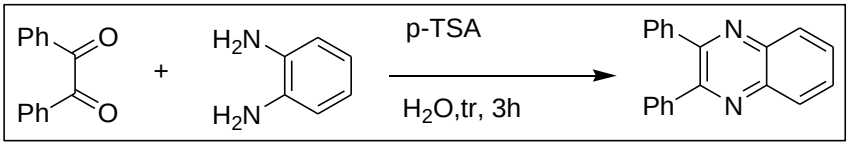
Scheme. Ⅰ.A. 14. Synthesis of pyrazine by 2H-azirines with α-diazo oxime ethers by N.S.Y. Loy et al (2015)

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



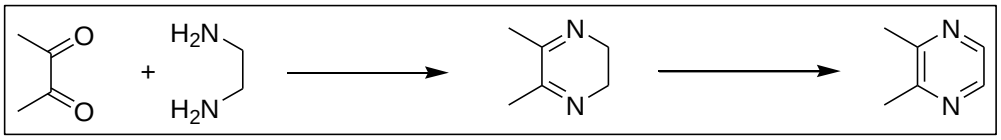
Scheme. Ⅰ.A. 15. Synthesis of benzopyrazine by Hazarika et.al (2007)

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



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

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

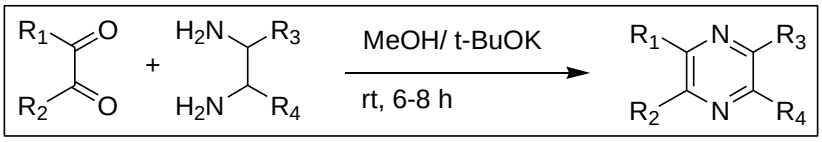


Scheme. Ⅰ.A. 17. Straight forward synthesis of pyrazine

Green approach in synthesizing pyrazine

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

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



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

Ⅰ.A.6. Conclusion

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

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

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

. the design of energy efficient processes

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

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

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

Ⅰ.A.7. References

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