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REVIEW PAPER

Review on the Synthesis of Pyrazine and Its Derivatives

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ABSTRACT

Pyrazine is a kind of natural product which can be found in plants, animals, insects, marine organisms and microorganisms. The main function of pyrazine in living organisms is used as flavor of the raw foods. Pyrazine and its derivatives were also produced in industries mainly for fragrance, flavor and pharmaceutical applications. This review describes the historical development of pyrazine including the discovery and synthesis, to the recent synthetic approach of pyrazinium. In general, six synthetic approaches namely condensation reaction, ring closure, metal catalysis, green reaction, Maillard reaction and acid catalyst on *N*-substitution have been reviewed in this paper. The first five approaches are mainly aimed for the substitution at 2, 3, 5 and 6 positions in pyrazine ring, whereas the last approach is specifically for 1 and 4 positions in pyrazine.

Keywords: Diazine, pyrazine, and Maillard reaction

INTRODUCTION

Diazine is described as a compound with monocyclic aromatic ring that contains two nitrogen atoms with a molecular formula of $C_4H_4N_2$. The three isomers of diazine are pyridazine, pyrimidine and pyrazine (Figure 1).

Pyrazine, or more commonly known as 1,4-diazine, refers to the 6 membered heterocyclic compounds with two nitrogen atoms in *para* position. This heteroaromatic compound is 6π-electron-deficient and resembles in planar configuration. Pyrazine exhibits inductive resonance properties (Figure 2) and demonstrates 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 *para* position (Sato, 2014). The specific dissociation constant for pyrazine are pK_{a1}= 0.65 and pK_{a2}= -5.78 (Dolezal & Zitko, 2015).

OCCURRENCES

Pyrazine can be found ubiquitously in nature but only in relatively low quantity (Müller & Rappert, 2010). Naturally occurring pyrazine is regarded as an important component that contributes greatly to the flavor of raw and processed food (Maga, 1992). Synthetic pyrazine derivatives are actively utilized not only in fragrance and flavor industry, but also in pharmaceutical industry (Maga, 1992).

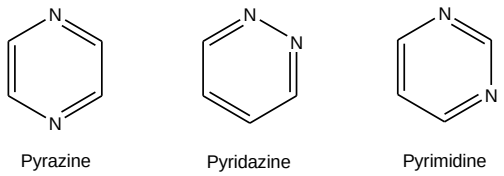


Figure 1. Isomers of diazine.

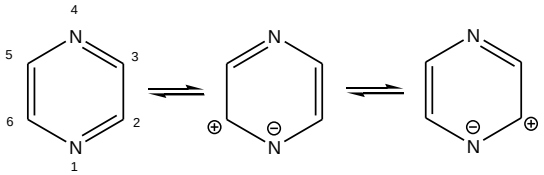


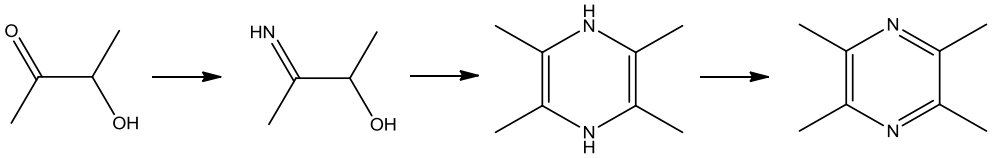
Figure 2. Inductive effects of pyrazine.

Pyrazine are produced naturally by living organisms including plants, animals, insects and marine organisms as well as microorganisms (Dolezal & Zitko, 2015). 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. In fact, Attygalle and Morgan (1984) reported that mixture of 2,5-dimethylpyrazine and 3-ethyl-2,5-dimethylpyrazine was excreted by ant *Tetramorium caespitum* (L.) to serve as trail pheromone. Besides, Showalter *et al.* (2010) confirmed that 2,5-dimethyl-3(2-methylbutyl)pyrazine is the mandibular alarm pheromone excreted by fire ant *Wasmannia auropunctata*. Apart from that, Müller and Rappert (2010) reviewed that pyrazine can be produced naturally through fermentation with the aid of microorganism. In year 1962, Kosuge and Kamiya discovered that tetramethylpyrazine, which was isolated from *Bascillus subtilis* has a distinct fermented soybean aroma. In addition, the Kosuge's group also reported about the formation of tetramethylpyrazine from acetoin through biosynthetic mechanism (Scheme 1) (Kosuge *et al.*, 1962). Besson *et al.* (1997) successfully optimized the production of tetramethylpyrazine from the bacterial *Bacillus natto* through solid state cultivation on soybeans. Besides that, mutant *C. glutamicum* and *L. diacetilactis* FC1 were reported to produce tetramethylpyrazine as well (Demain *et al.*, 1967; Kim & Lee, 1991). Furthermore, Gallois and Grimont (1985) reported that *Serratia* and *Cedecea* strains were able with produce several pyrazine compounds that contribute to the potato-like aroma. In 2005, Dickschat and co-workers managed to identify a total of 27 pyrazines from the extract of myxobacterium *Chondromyces crocatus* including a novel pyrazine, 2,5-dimethyl-3-(methylsulfanyl)pyrazine.

Besides, those pyrazine compounds such as 2-methoxy-3-*sec*-butylpyrazine, 2-methoxy-3-iso-butylpyrazine, 2-methoxy-3-iso-propyl-pyrazine can be found in galbanum oil, beans, beetroot, lettuce, nasturtium and green pepper bell (Bramwell *et al*., 1969; Murray *et al.*, 1970). Pyrazine can be generally found in heat processed food as it is formed through Maillard reaction (more details can be found in the Section called "Formation of pyrazine through Maillard reaction") (Nursten, 2005). Alkylpyrazine can be found in most of roasted food such as coffee, cocoa, peanut and roasted beef (Cheeseman & Werstiuk, 1972). Meanwhile, 2-acetylpyrazine was associated to the popcorn aroma as claimed by Müller and Rappert (2010). Czerny and Grosch (2000) reported that 2-methoxy-3-isobutylpyrazine, 2-methoxy-3,5-dimethylpyrazine and 2-methoxy-3-isopropylpyrazine were among the dominant odorant found in raw Arabica coffee. The study concluded that the 2-methoxy-3-isobutylpyrazine showed the highest odor activity among the extracted chemicals from the Arabica coffee bean before and after the roasting process (Czerny & Grosch, 2000). Allen and Lacey (1998) reported that 2-methoxy-3-isobutylpyrazine, 2-methoxy-3-*sec*-butylpyrazine and 2-methoxy-3-isopropylpyrazine play significant role in the unique aroma of wine, especially the wine derived from grape.

HISTORY OF PYRAZINE SYNTHESIS

The pyrazine synthesis was first reported by Laurent in 1844 whereby it was later confirmed to be 2,3,5,6-tetraphenylpyrazine in 1897 by Snape and Brooke (Figure 3). Laurent named the compound as "amarone". The "amarone" was prepared by dry distillation of α-phenyl-α-(benzylideneamino) acetonitrile, PhCH=NCHPhCN (Snape & Brooke, 1897).



Scheme 1. Biosynthetic mechanism of tetramethylpyrazine from acetoin proposed by Kosuge *et al*. (1962).

Ever since then, various derivatives of pyrazine were produced. However, it was until 1882, Wleügel was the first to propose that pyrazine composed of six-membered ring analogous to pyridine. In 1887, Mason and Wolff separately suggested that the word "pyrazine" can be utilized for the compound mentioned above (Mason, 1889). The author clarified that a six-membered ring compound, which is made up of four carbon and two nitrogen atoms, was classified as diazine. The diazines are further categorized into *o*-diazine, *m*-diazine as well as *p*-diazine, and they are called oiazine, miazine, and piazine, respectively. However, the designated naming did not gain adoption although it had been well promoted by Mason (1889). On the other hand, the term pyrazine gained better acceptance by the science community.

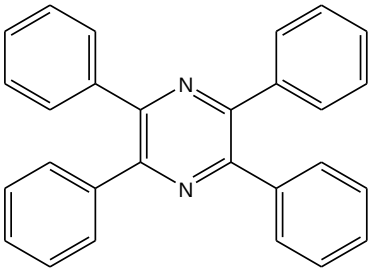


Figure 3. 2,3,5,6-tetraphenylpyrazine which first synthesized by Laurent in 1844.

It is noteworthy that in 1897, Snape and Brooke concluded that the previously reported compound amarone, benzoinimide, ditolanazotidea and tetraphenylazine, all belonged to the same compound, which is tetraphenylpyrazine (Japp & Wilson, 1886; Japp & Burton, 1887; Snape & Brooke, 1897). Despite that, the actual structure of pyrazine has not yet been established. During that period, the chemistry community was debating on the possible bond structure of pyrazine, either it was Kekulé type or Dewar type arrangement (Figure 4). Kekulé type refer to the conjugated double bond within the pyrazine molecule while Dewar type refers to the long para bond that bound the two nitrogen atoms.

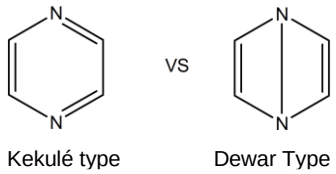


Figure 4. The proposed Kekulé and Dewar type of pyrazine.

Japp and Burton (1887) proposed the Dewar type pyrazine by concluding that the azine they have produced resembled Dewar type configuration (Figure 5). It was further supported by Mason and coworkers also about the fact that pyrazine existed in Dewar type arrangement (Mason & Dryfoos, 1893; Mason, 1893; Mason & Winder, 1893). After the analysis of molecular refraction of various pyrazine derivatives, Bruhl finally validated that the pyrazine existed in Kekulé configuration (Krems & Spoerri, 1947; Barlin, 1982). With the aid of X-ray diffraction crystallography, Schomaker and Pauling (1939) studied the interatomic distances of various compounds including pyrazine. They compared pyrazine to pyridine and found out that both of C-N bonds were almost similar in length, 1.35 ± 0.02 Å and 1.37 ± 0.03 Å, respectively. These C-N bond values were slightly larger than the expected Kekulé resonance due to the electron delocalization present in the ring. They suggested that the extra resonance with ionic structure contributing to the observed phenomena (Schomaker & Pauling, 1939). On the other hand, Wheatley (1957) utilized X-ray analysis to determine the structure of pyrazine. From the analysis, the author confirmed that the C-C, C-N and C-H bond were 1.378 Å, 1.334 Å and 1.050 Å, respectively (Wheatley, 1957). Bormans *et al*. (1977) reinvestigated the molecular structure of pyrazine using gas-phase electron diffraction and compared it with benzene and pyridine. The authors concluded that C-C bond of pyrazine was slightly greater than benzene but similar to pyridine. Whereas, the C-N bond of pyrazine and pyridine were the same within the margin of error. It is noteworthy that the C-H bond of pyrazine is longer compared to benzene and pyridine (Bormans *et al*., 1977).

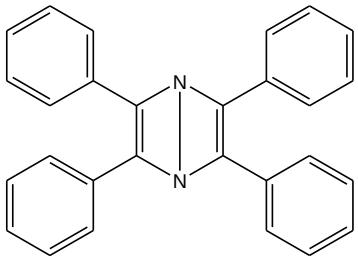


Figure 5. The postulated pyrazine structure by Japp and Burton (1887).

PREPARATION OF PYRAZINE

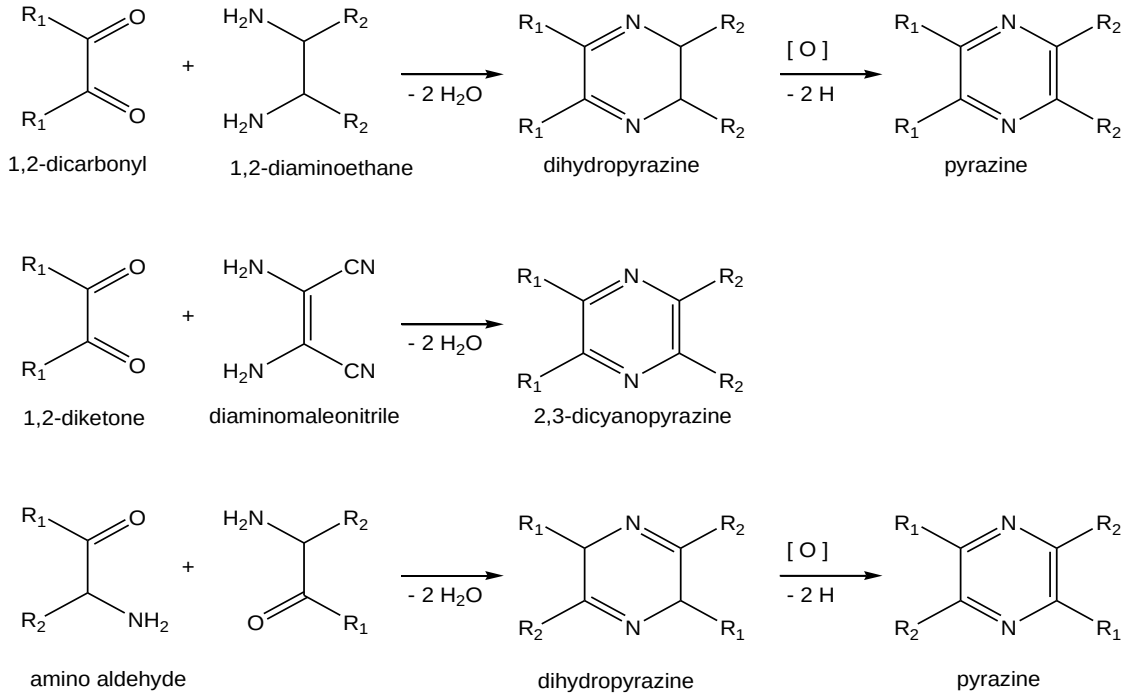
Classical preparation of pyrazine

Pyrazine can be conveniently prepared from oxidation of dihydropyrazine, which was the condensation product of 1,2-dicarbonyl with 1,2-diaminoethane (Scheme 2) (Gilchrist, 1997). Copper (II) oxide and manganese oxide are commonly used as oxidizing agents for dihydropyrazine. Eicher *et al*. (2003) suggested that symmetrical starting compound give the best results from the previous reaction. The authors reported that the reaction of diketone and diaminomaleonitrile to give pyrazine.

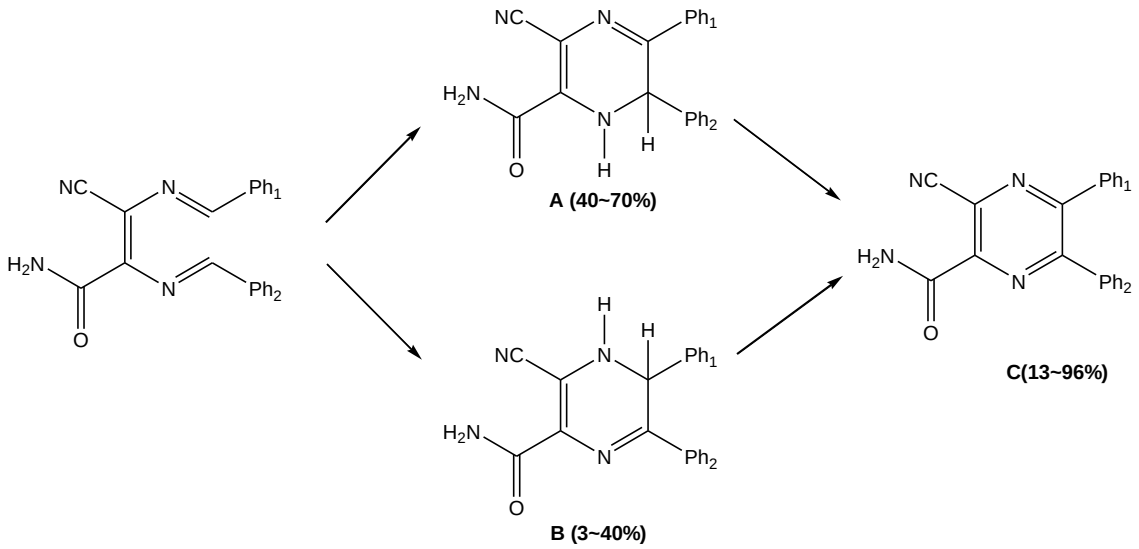
Besides that, pyrazine can be produced from self-condensation of two moles of α-aminocarbonyl to give 3,6-dihydropyrazine, followed by oxidation under mild condition.

Formation of pyrazine through ring synthesis

Ohtsuka *et al.* (1979) reported an alternative route to synthesize pyrazine through cyclization of 2,3-bis(arylideneamino)-3- cyanoarylamides to form pyrazine precursor 1,2-dihydropyrazine (Scheme 3). The starting material, 2,3-bis(arylideneamino)-3-cyanoaryl-amides was heated in DMSO for a short period of time followed by crystallization from hot benzene to give 1,2-dihydropyrazine A and B, which can be easily distinguished *via* TLC, melting point and other analytical instruments. The study suggested that the hydrogen bond formed between the aromatic NH and $CONH_2$ could stabilize compound A, thus, a higher yield of 1,2-dihydropyrazine A was isolated compared to 1,2-dihydropyrazine B (Ohtsuka *et al*. 1979).

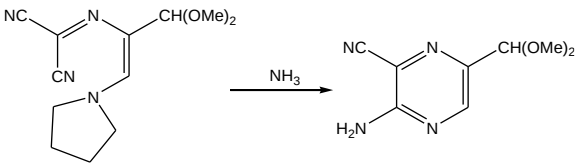


Scheme 2. Classical formation of pyrazine.



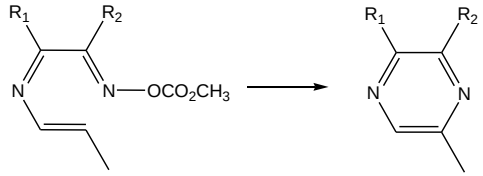
Scheme 3. Formation of pyrazine through cyclization reported by Ohtsuka *et al*. (1979).

Taylor and Dumas (1981) reported the reaction of dicyanide with ammonia could access the formation of pyrazine as well (Scheme 4). It was demonstrated by the reaction between 3,3-dimethoxy-1-(pyrrolidin-1-yl)prop-1-en-2-yl)carbonimidoyl dicyanide and ammonia in MeOH solution has successfully afforded 2-amino-3-cyano-5-(dimethoxy-methyl)pyrazine at 31% yield.



Scheme 4. Formation of 2-amino-3-cyano-5-(dimethoxymethyl) pyrazine reported by Taylor and Dumas (1981).

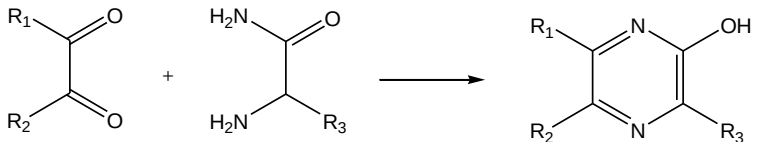
Later in the year 1991, Büchi and Galindo reported the regioselective formation of alkylpyrazines, which started from the condensation of allylamines and α-oximido carbonyl. The resulted imines underwent isomerization in the presence of potassium *tert*-butoxide followed by *o*-acylation with methyl chloroformate to produce carbonate, which was then subjected to thermal electrocylization-aromatization in toluene at 300°C to yield pyrazines at 60% (Scheme 5). It was concluded that both *E* and *Z* isomers act as precursor for pyrazine at 300°C (Büchi & Galindo, 1991).



Scheme 5. Therma electrocylization-aromatization of carbonate to produce pyrazine.

Formation of pyrazine through condensation

In year 1949, Jones discovered the pyrazine derivatives synthesis pathway that involved condensation of α-amino acid amides and 1,2-dicarbonyl (Scheme 6). Jones (1949) concluded that the reaction pathway was more direct, convenient and higher yield can be easily isolated. The author conducted the reaction in methanol in the presence of sodium hydroxide. Generally, the condensation of unsymmetrical dicarbonyl and α-amino acid amides are expected to give at least two isomers. However, Jones (1949) successfully isolated single compound from the reaction of α-amino acid with methylglyoxal or phenylglyoxal to give pyrazine.



Scheme 6. Reaction pathway reported by Jones (1949).

Ten years later, Vogl and Taylor (1959) reported the reaction between α,β-dicarbonyl and aminomalonamidamidine dihydrochloride (Scheme 7) could be used to access pyrazine derivative. The reaction between aminomalonamidamidine dihydrochloride and dry glyoxal bisulphate in the presence of dilute ammonium hydroxide at 0-20°C gave 76% of 2-aminopyrazine-3-carboxamide. Glyoxal bisulphate was chosen as the starting material instead of glyoxal because the reaction was very slow if commercial glyoxal was employed. The reaction between methylglyoxal and phenylglyoxal and aminomalonamidamidine dihydrochloride was carried out and both reactions could end up with a good yield of more than 60%.

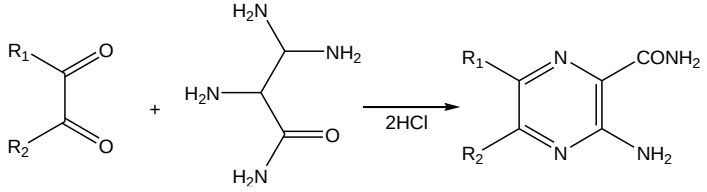
Begland *et al.* (1974) reported the condensation reaction of diiminosuccinonitrile and diaminomaleonitrile in the presence of strong acid. The strong acid was used to protonate the diiminosuccinonitrile and promote elimination of ammonia. Different amounts of strong acid produced three different pyrazine products. The use of one equivalent of acid led to aminotricyano-pyrazine, while excess amount of acid gave tetracyanopyrazine. The reaction using catalytic amount of acid gave 2,3-diamino-5,6-dicyanopyrazine (Scheme 8). The study pointed out that the use of catalytic amount of acid catalyzed the cycloaddition of diaminomaleonitrile to diiminosuccinonitrile.

A couple of years later, Keir *et al.* (1978) reported the condensation of 1,2-dicarbonyl with ethyl-2-amidino-2-aminoacetate dihydro-chloride to yield pyrazine (Scheme 9).

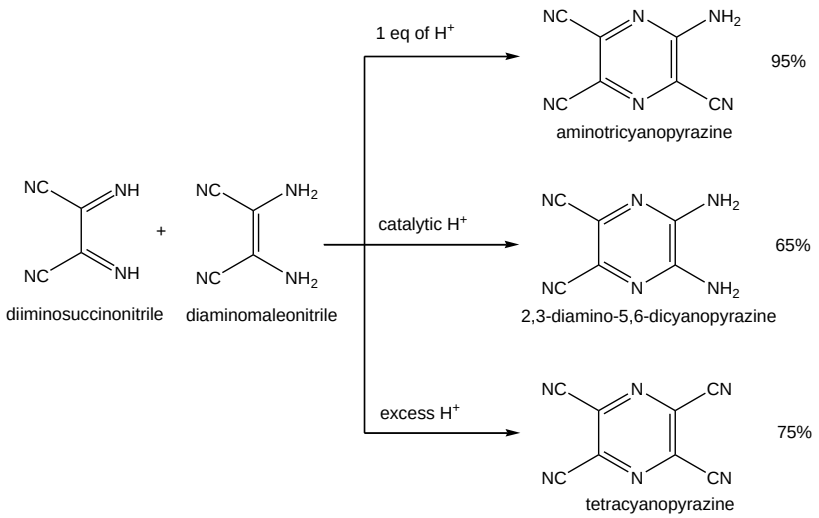
The reaction of symmetrical glyoxal with ethyl 2-amidino-2-aminoacetatedihydro-chloride at 10°C in the presence of sodium acetate gave 22% of ethyl-3-amino-pyrazine-2-carboxyl-ates. Meanwhile, the reaction between ethyl-2-amidino-2-aminoacetate and symmetrical diacetyl yielded 61% of ethyl-3-amino-5,6-dimethyl-pyrazine-2-carboxylates.

Ohta *et al.* (1979) reported the condensation of phenylglyoxal with propylenediamine followed by dehydrogenation in the presence of sodium hydroxide to give a mixture of 2-methy-l,5-phenylpyrazine and 2-methyl-6-phenylpyrazine (Scheme 10). The mixture was separated by a column chromatography eluting with hexane-ether (7:3) to give 2-methyl-6-phenylpyrazine while elution with hexane-ether (3:7) gave 2-methyl-5-phenylpyrazine.

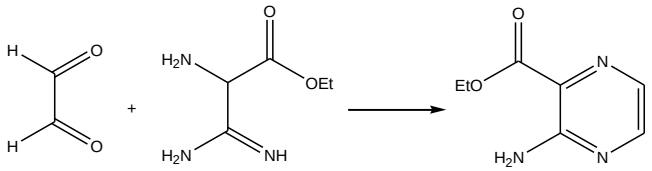
Fukunaga and Begland (1984) demonstrated that the [4+2] cycloaddition of diiminosuccinonitrile with electron rich compound such as 1,2-dimethoxyethylene and ynamines could give pyrazine as well (Scheme 11). The study showed that the reaction between diiminosuccinonitrile and 1,2-dimethoxyethylene occurred exothermically to give 76% of 2,3-dimethoxy-5,6-dicyano-1,2,3,4-tetrahydropyrazine and concluded that the cycloaddition reaction was at least 98% stereospecific. The tetrahydropyrazine lost its methanol through heating or on silica gel to yield 2,3-dicyanopyrazine. The study was continued with the reaction between diiminosuccinonitrile and ynamines such as phenyl(diethylamino)-acetylene and diethyl-amino-1-propyne resulting in 50-60% of purified pyrazine.



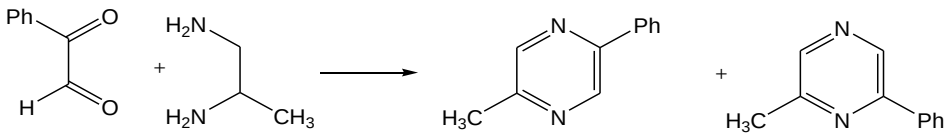
Scheme 7. Formation of pyrazine reported by Vogl and Taylor (1959).



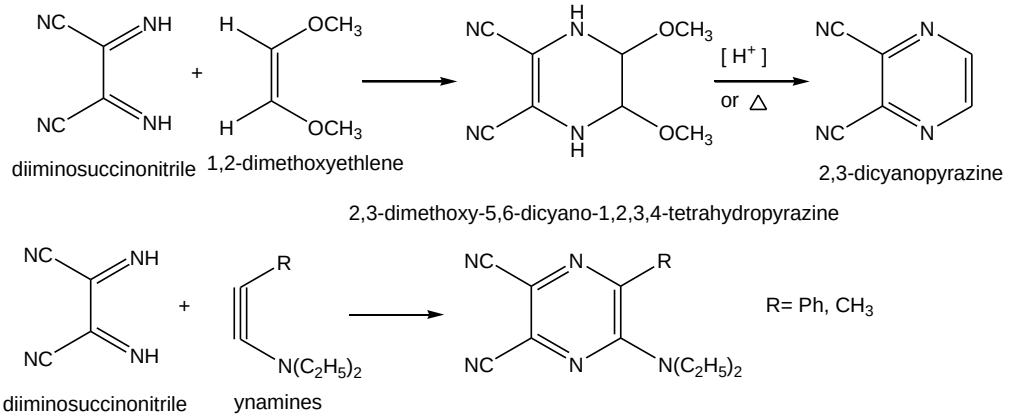
Scheme 8. Reaction of diiminosuccinonitrile and diaminomaleonitrile reported by Begland *et al*. (1974).



Scheme 9. Formation of pyrazine reported by Keir *et al*. (1978).



Scheme 10. Formation of pyrazine reported by Ohta *et al*. (1979).



Scheme 11. Formation of pyrazine reported by Fukunaga and Begland (1984).

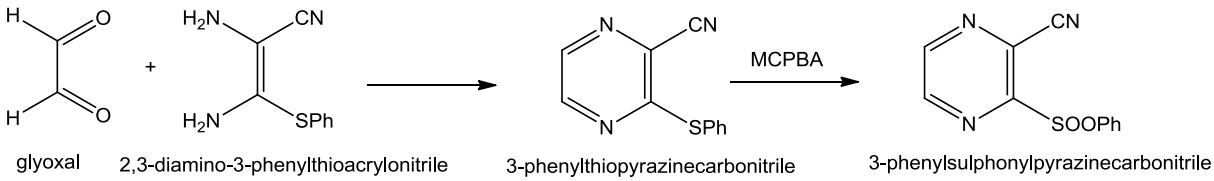
In 1994, Tazaki *et al.* patented a reaction pathway whereby glyoxal condensed with 2,3-diamino-3-phenylthioacrylonitrile to give 3-phenylthiopyrazinecarbonitrile (Scheme 12). The starting material of 2,3-diamino-3-phenylthioacrylonitrile could be prepared from the reaction between diphenyl disulphide and hydrogen cyanide. The sulphide functional group was readily oxidized to 3-phenylsulphonylpyrazinecarbonitrile in the presence of *m*-chloroperbenzoic acid (MCPBA) under mild condition.

Seven years later, Zhang *et al.* (2001) repeated the above reaction using phenylglyoxal and found that the product was a mixture of 5-phenyl-3-phenylthiopyrazine-carbonitrile and 6-phenyl-3-phenylthio-pyrazinecarbonitrile without any selectivity. Thus, instead of phenylglyoxal, Zhang *et al.* (2001) utilized 2,2-diethoxyacetophenone to react with 2,3-diamino-3-phenylthio-acrylonitrile to give a similar mixture (Scheme 13). High selectivity of 6-phenyl-3-phenylthio-pyrazinecarbonitrile could be produced in a good yield (86%) from the reaction with the presence of excess trifluoroacetic acid (TFA).

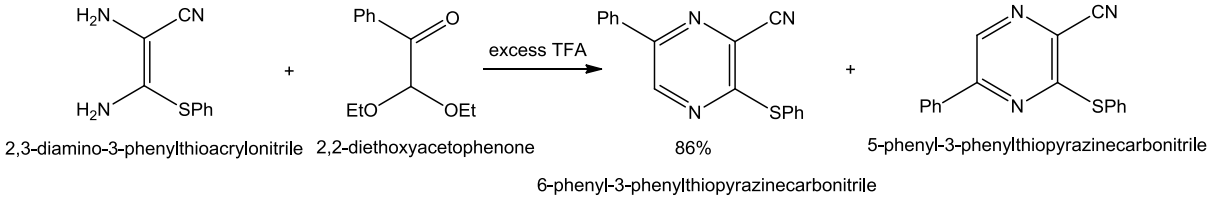
This synthetic approach continued as a method of options among chemists to access pyrazine and its derivatives after 2001. In fact, in the latter development, the pyrazine derivatives were mainly synthesized using substitution reaction of pyrazine to other organic compound analogues such as the preparation of *ortho*-linked oxacalix-[2]-benzene-[2]-pyrazine (Scheme 14) as reported by Kong *et al.* (2012).

Formation of pyrazine with the aid of metal

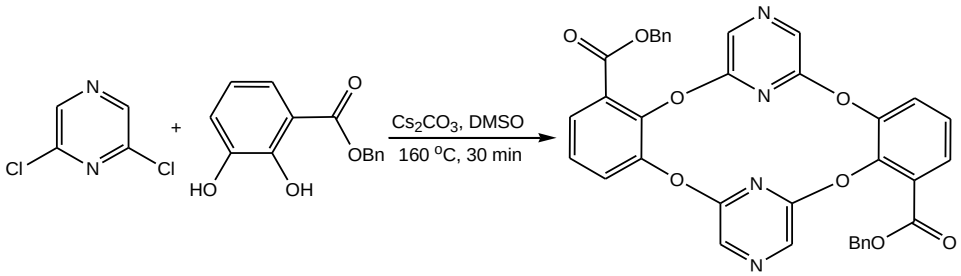
Pyrazine could also be synthesized in the presence of metal catalyst. Higasio and Shoji (2001) reviewed that Okada was the first to report the synthesis of pyrazine through vapor phase reaction of diamine with diols in the presence of granular alumina as the catalyst. Other catalytic systems such as silver, copper-chromium, zinc-phosphoric acid-manganese and copper-zinc-chromium were also reviewed. However, most of the above mentioned catalytic systems were patented and the available patent data were limited. Nevertheless, several literatures related to the catalytic formation of pyrazine could still be found and were reported herein.



Scheme 12. Reaction of glyoxal with 2,3-diamino-3-phenylthioacrylonitrile reported by Tazaki *et al*. (1994).



Scheme 13. Reaction of 2,3-diamino-3-phenylthioacrylonitrile with 2,2-diethoxyacetophenone reported by Zhang *et al*. (2001).



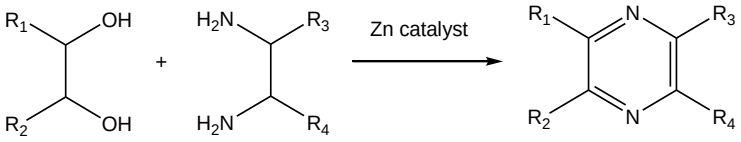
Scheme 14. Synthesis of *ortho*-linked oxacalix[2]benzene[2]pyrazine (Kong *et al*., 2012).

Anderson *et al.* (1967) studied the deamination of diethylenetriamine in the presence of kaolin and alumina. The study managed to produce 27.5% of pyrazine using a mixture of catalyst Al_2O_3:MoO_3:P_2O_5 in the ratio of 94:5:1 and yielded maximum selectivity in producing pyrazine without the presence of other side products.

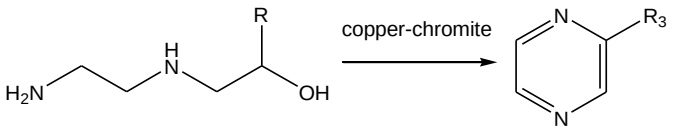
Sato patented the reaction pathway to synthesize pyrazine in the presence of zinc (U.S. Patent No. 4,097,478, 1978). The reaction between diamine and diol in the presence of zinc as the catalyst through gas phase contact reaction at 300-600°C by utilizing silica, alumina or silica-alumina as the carrier for the catalyst was successfully afforded pyrazine at 55-78% yield (Scheme 15). Zinc oxide or a mixture of 10% zinc with other metals such as cobalt, nickel, iron, aluminum and chromium could be used as the catalyst for reaction.

In 1990, Lee *et al.* patented the synthesis of pyrazine using copper-chromite catalyst (Scheme 16) (U.S. Patent No. 4,966,970, 1990). It was claimed that the reaction could produce more than 90% of yields with up to 97% of conversion. The catalytic reaction was carried out by adding copper-chromite catalyst to diamine compound at 300-450°C for 1-3 hours. The proposed optimum temperature was recommended as an essential key for the success of the reaction. When the reaction was carried out at <300°C, there were more incomplete dehydrogenated product, which was piperazine instead of pyrazine. On the other hand, several by-product were produced from the breaking down of pyrazine when the reaction temperature exceeded 450°C.

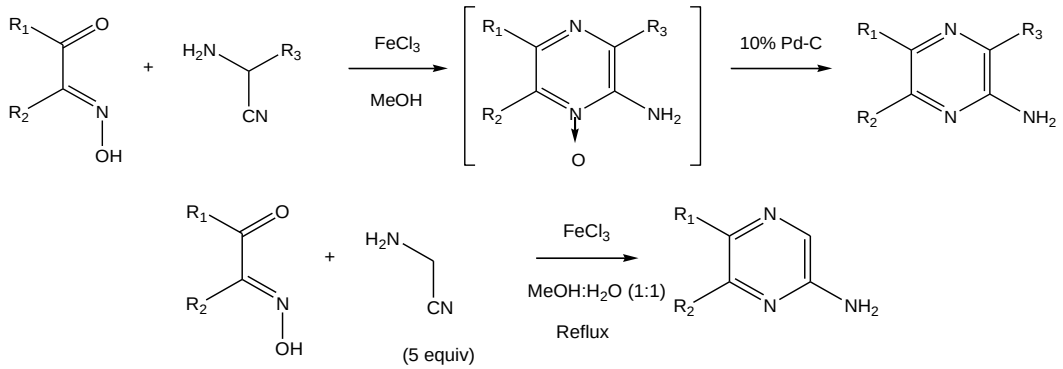
In year 2002, Itoh *et al.* reported the catalytic activity of $FeCl_3$ in producing pyrazine. The reaction between isonitroso-acetophenone and aminoacetonitrile was carried out in the presence of one equivalent of $FeCl_3$ to give *N*-oxide pyrazine and subsequent hydrogenation with 10% of Pd-C to afford 55-80% pyrazine (Scheme 17). One step catalytic reaction was studied between isonitrosoacetophenone and five equivalents of aminoacetonitrile in the presence of $FeCl_3$ to give 65-72% of pyrazine. This straightforward preparation generally gave better results compared to the two steps of reaction mentioned earlier.



Scheme 15. Formation of pyrazine in the presence of zinc reported by Sato (1978).



Scheme 16. Synthesis of pyrazine using copper chromite reported by Lee and co-workers (U.S. Patent No. 4,966,970, 1990).



Scheme 17. Catalytic formation of pyrazine using $FeCl_3$ reported by Itoh *et al*. (2002).

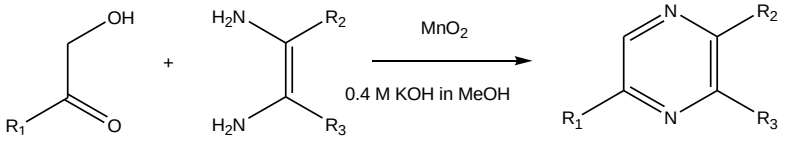
A year later, Richard (2003) reported the catalytic formation of pyrazine using excess manganese dioxide (Scheme 18). The reaction between α-hydroxylketones and 1,2-diamino was performed in the presence of manganese dioxide. The addition of KOH in methanol was essential to the reaction mixture and could give 10-66% of pyrazine.

In the same year, Park *et al.* (2003) demonstrated the cyclization of propyleneglycol and ethylenediamine to give 2-methylpyrazine using $CuO\text{-}SiO_2$, $ZnO\text{-}SiO_2$ and $CuO\text{-}ZnO\text{-}SiO_2$. The authors concluded that $CuO\text{-}ZnO\text{-}SiO_2$ catalyst showed the best efficiency among the three catalysts tested. Park and co-workers believed that the great performance of the $CuO\text{-}ZnO\text{-}SiO_2$ (3:6:1) catalyst was attributed to the combined effect of dehydrogenation properties of $CuO\text{-}SiO_2$ and cyclization properties of $ZnO\text{-}SiO_2$. The $CuO\text{-}ZnO\text{-}SiO_2$ exhibited remarkable catalytic activity in dehydrocyclization of propyleneglycol and ethylenediamine to yield of 84% of 2-metylpyrazine with conversion of over 99%.

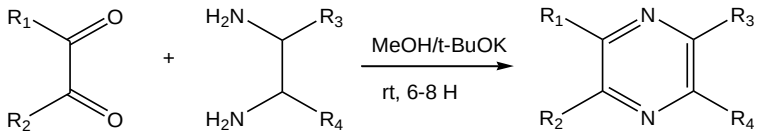
Latha *et al.* (2007) carried out the synthesis of pyrazine using ethylenediamine in the presence copper oxide-copper chromite catalyst. The catalyst showed promising result with more than 98% selectivity over the temperature range of 340-440°C. They believed that two moles of ethylenediamine underwent cyclization with elimination of ammonia molecule to give piperazine, followed by dehydrogenation to yield pyrazine. The combination of $CuO\text{-}CuCr_2O_4$ with ratio of 2:1 showed 85% of conversion with more than 98% of pyrazine selectivity.

Green approach in producing pyrazine

Pyrazine can be synthesized from various reaction methods, but the main drawbacks in most of the reactions are poor reaction yield, long reaction time, requirements of toxic solvents as well as metals, and complicated work up processes. In this modern era, where green chemistry is becoming more and more vital, eco-friendly method in synthesizing pyrazine has been developed to confront the challenge. Thus, Ghosh and Mandal (2012) successfully developed an environmentally benign protocol for producing pyrazine (Scheme 19). The protocol involved a simple condensation of 1,2-diamine and 1,2-dicarbonyl in the presence of potassium *tert*-butoxide at room temperature to obtain 72-88% of pyrazine. It was concluded that the reaction proceeded with the formation of dihydroprazine followed by aromatization to give pyrazine.



Scheme 18. Catalytic formation of pyrazine reported by Richard (2003).



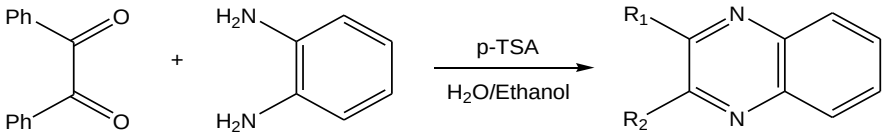
Scheme 19. Green approach in producing pyrazine reported by Ghosh and Mandal (2012).

In 2007, Hazarika *et al.* reported an environmentally friendly protocol in producing quinoxaline (Scheme 20). Quinoxaline is also known as benzopyrazine, which is a derivative of pyrazine. The reaction between 1,2-diketone and *o*-phenylenediamine in the presence of 10 mol% of indium chloride. The reaction was performed in aqueous solution at room temperature to afford 88-98% yield.

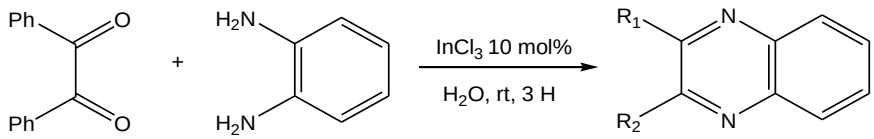
Seven years later, Mahadik *et al.* (2014) utilized an ultrasonic wave technique in producing quinoxaline from the mixture of *o*-phenylenediamine and benzil in the presence of *p*-toluenesulfonic acid (*p*-TSA) (Scheme 21). Even though, the mixture was subjected to sonication for 8 minutes, 97% yield of 2,3-diphenylquinoxaline could be obtained. This protocol offered a shorter reaction time, higher yield, milder reaction condition and minimum generation of toxic waste products compared to conventional methods.

Formation of pyrazine through Maillard reaction

Besides the previously mentioned synthesis methods, pyrazine can be produced from the Maillard reaction. The reaction pathway was discovered and named after Louis-Camille Maillard (Nursten, 2005). The Maillard reaction is a non-enzymatic browning of food that involves condensation of carbonyl compound and amine, which are reducing sugar and amino acid, respectively. This reaction often initiated upon heating process or extended storage period of food. However, the Maillard reaction remained relatively complex and complicated because it could produce a large variety of pyrazine (Adams *et al.*, 2008). It was reported that Maillard browning reaction contributes to the unique roasted aroma, taste, color and nutritional value of heated food (Nursten, 2005). Scalone *et al.* (2015) proposed that the general mechanism in producing pyrazine through the Maillard reaction starts with condensation of dicarbonyl compound (from degradation of reducing sugar) and amino acid. Strecker aldehyde and α-aminoketones were formed after decarboxylation of the condensed product through cyclic transition state. Then two molecules of α-aminoketones underwent condensation to give dihydropyrazine. The dihydropyrazine could either undergo oxidation to give pyrazine or deprotonation then combined with Strecker aldehyde to give another derivative of pyrazine (Scalone *et al.*, 2015).



Scheme 20. Formation of quinoxaline reported by Hazarika *et al.* (2007).



Scheme 21. Formation of quinoxaline reported by Mahadik *et al.* (2014).

Amrani-Hemaimi *et al.* (1995) studied the alkylpyrazine formation from the reaction of glucose and fructose with ^{13}C-labelled alanine and ^{13}C-labelled glycine. The reaction mixture was heated at 180°C for 7 minutes and more than 11 pyrazine derivatives were detected. It was concluded that different types of reducing sugar did not possess significant effect on the pyrazine formation. However, the type of amino acid used has a greater impact on the number of pyrazine produced because there were only six derivatives of pyrazine detected when glycine reacted with either glucose or fructose. There were more than 11 pyrazine derivatives formed when alanine was used as the starting material. Some pyrazine formed did not have any labelled ^{13}carbon while other derivatives such as 3-ethyl-2,5-dimethylpyrazine have 100% ^{13}carbon labelled at the substituted ethyl group. Amrani-Hemaimi *et al.* (1995) suggested that the 3-ethyl-2,5-dimethylpyrazine was formed through the reaction of 2,5-dimethyl dihydropyrazine with ^{13}carbon labelled formaldehyde that comes from alanine. On the other hand, Scalone *et al.* (2015) studied the involvement of peptide in the formation of pyrazine through the Maillard reaction. More than 8 derivatives of pyrazine were detected from the reaction. Oligopeptide from hydrolyzed whey protein significantly increased the production of pyrazine during the Maillard reaction. It was reported that the free amino acid resulted from the hydrolysis of whey protein does not play major role in pyrazine formation. Scalone *et al.* (2015) concluded that the higher yield of pyrazine was observed when the reaction was carried out in roasting condition at 180°C for 90 minutes.

N-substituted pyrazine

Quaternary is the terminology used by scientist to distinguish central carbon atoms attached to another four carbon atoms (Klein, 2011). It is impossible for alcohol and alkyl halide to have quaternary structure as this disobeys the octet rule. On the other hand, amine has the ability to form quaternary compound as it has extra lone pair electron on the nitrogen atom. Tertiary amine can undergo alkylation to form quaternary ammonium salt with positive charge on the nitrogen atom.

Duffin (1964) claimed that diquaternization of heterocyclic compound is theoretically possible. More research on this concept has been carried out and the development of new techniques and novel methodologies to access this target continue to evolve. In 1950, Bahner and Norton obtained monoquanternized pyrazine by reacting pyrazine with excess phenacyl bromide. Blood and Noller (1957) attempted to produce diquaternary salts of pyridazine with excess ethyl bromide or methyl iodide at 100°C. However, their efforts also ended up with monoquaternary salts of pyridazine. Blood and Noller (1957) explained that the failure might be due to the positive charge of the compound upon the first quaternization. In fact, Chia and Trimble Jr (1961) estimated that the first and second dissociation constants of pyrazine were differed by 10^6. Gao and Jean'ne (2004) proposed that the failure to diquaternize pyrazine related to the significant reduction of nucleophilicity of the system after quaternization of one of the nitrogen atom.

In 1965, Curphey established a new technique to synthesize and purified diquaternary pyrazine. In this approach, the diquaternary pyrazine salt was prepared by refluxing pyrazine and triethyloxonium fluoroborate in dichloroethane. The reaction generally gave high yield (6~97%) of diquaternary pyrazine derivatives. The preparation of diquaternary pyrazine was described in detail by Curphey and Prasad in their literature published in year 1972. The study proposed the use of base-fused trimethyloxonium tetrafluoroborate in dichloroethane for the diquaternary process as it helps to promote homogeneous reaction with pyrazine (Figure 6).

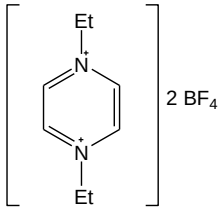
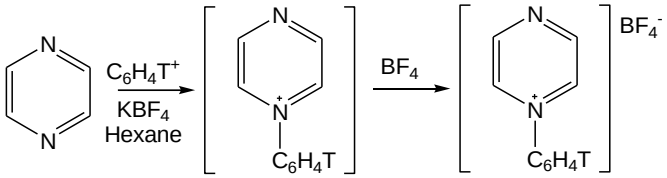


Figure 6. Diquaternary pyrazine reported by Curphey & Prasad (1972).

Later, Alberti and Hudson (1983) reported the unexpected formation of pyrazinium cation during their investigation of free radicals. The study showed the formation of *N*,*N*'-di-*tert*-butylpyrazinium cation when 1,4-diaza-1,3-butadiene reacted with metal halides $AsCl_2Ph$ and $SbCl_2Ph$.

Shchepina *et al.* (2015) reported the synthesis of tritium-labeled *N*-phenylpyrazium using free and highly reactive nucleogenic phenyl cation which was the tritium β-decay product of *para*-ditritiated benzene. However, the reaction could only give a relatively low yield (Scheme 22).



Scheme 22. Preparation of tritium-labelled *N*-phenylpyrazium reported by Shchepina *et al.* (2015).

CONCLUSION

All techniques described herein can be considered to prepare pyrazine and variety of pyrazine derivatives. Different synthetic approaches can be used for different substituents that are attached to the pyrazine ring. Among all of the reviewed approaches, the one for synthesizing pyrazinium cation attracted much attention due to its comprehensive synthetic methodology as well as the unique final product.

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