Chapter IV

Highly efficient polymeric-Cu (II) catalysed one pot multi-component synthesis of substituted N-heterocycles *via* double condensation/ tandem oxidation-cyclisation/elimination cyclisation reactions from diverse starting precursors under milder reaction conditions:

Section A

(General introduction and synthetic background)

IV. A. 1. A general introduction of pyrazine and quinoxaline and their synthetic background:

Pyrazine is an organic heterocyclic compound having molecular formula $C_4H_4N_2$. Structurally pyrazine hasa symmetrical moiety, with two nitrogen atoms at 1 and 4 positions respectively in a benzene ring (fig. IV. A. 1). They are important components of aroma fragrances and naturally found in fenugreek.

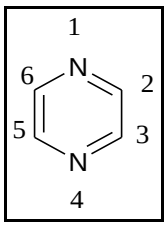


Fig. IV. A. 1. General structure of pyrazine moiety

Whereas quinoxaline has molecular formula $C_8H_6N_2$ and formed by the fusion of two aromatic rings benzene and pyrazine, hence they are also known as benzopyrazine. In quinoxaline two nitrogen atoms are present at 1 and 4 positions of a naphthalene ring (fig. IV. A. 2). It is an important class of biologically active moiety and acts as bioisoster of benzo-thiophene, naphthalene and quinoline.

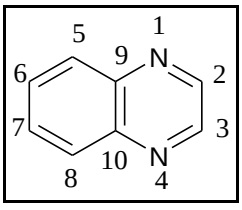


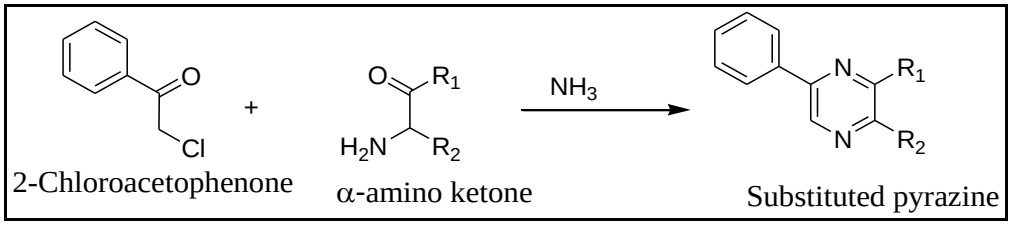
Fig. IV. A. 2. Quinoxaline moiety

IV. A. 2. Methods of preparation of pyrazine and quinoxaline:

There are a number of classical and modern methods for the synthesis of both pyrazine and quinoxaline from diverse precursor are available. Some of them are described below.

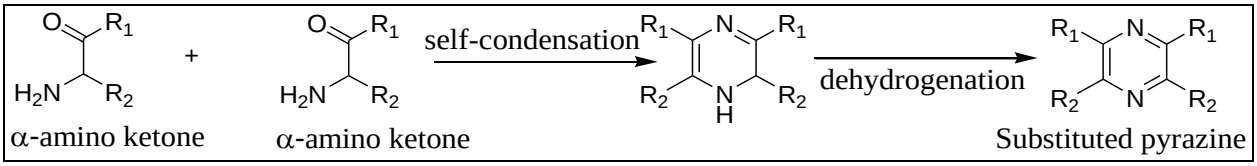
IV. A. 2. 1. Classical methods for pyrazine synthesis:

Classically, pyrazine was synthesized by the condensation- oxidation of 2-chloroacetophenone with α-amino ketone in presence of ammonia, given by Staedel–Rugheimer in 1876 (scheme. IV. A. 1).



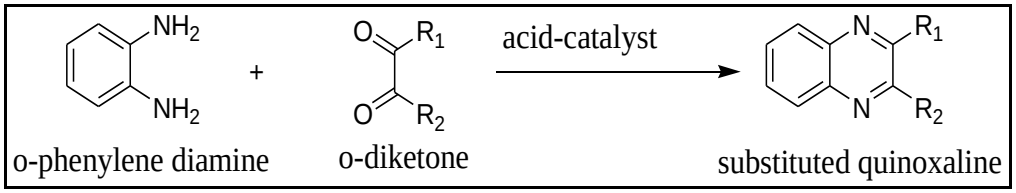
Scheme. IV. A. 1. Staedel–Rugheimer pyrazine synthesis.

Moreover, due to presence of lachrymatory agent 2-chloroacetophenone, Gutknecht in 1879 modified the technique in which self-condensation of α-amino ketones are takes place followed by dehydrogenation (scheme. IV. A. 2).



Scheme. IV. A. 2. Gutknecht process of pyrazine synthesis.

Similarly, quinoxaline is prepared by the condensation of α- dicarbonyl compounds with o-phenylene diamine in presence of an acid catalyst (scheme. IV. A. 3).



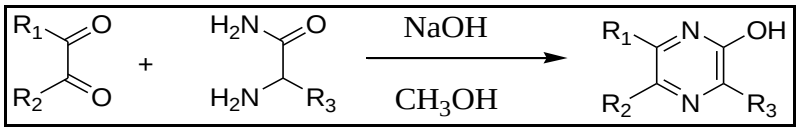
Scheme. IV. A. 3. Classical method of quinoxaline preparation

IV. A. 2. 2. Modern method of pyrazine and quinoxaline preparation:

As the classical route for preparation of pyrazine and quinoxaline gives quite satisfactory yield, but long reaction time, strong acidic medium and high temperature make the necessity to find a milder and acceptable method for their preparation. Literature survey reveals a numerous method for synthesis of pyrazine and quinoxaline.

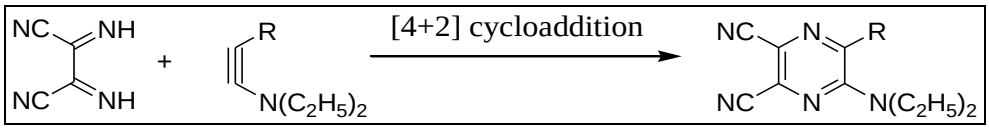
IV. A. 2. 2. 1. Modern method of pyrazine synthesis:

Since the method developed by Staedel–Rugheimer in 1876 a number of alternatives are reported for synthesis of pyrazine and their derivative using different precursor to achieve a milder reaction condition. Such as R.G. Jones in 1949 reported the condensation of α-amino acid amides and 1,2-dicarbonyl in presence of sodium hydroxide in methanol (scheme. IV. A. 4) [1].



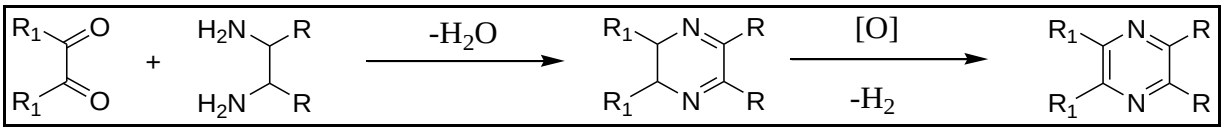
Scheme. IV. A. 4. Jones method of pyrazine synthesis

E.C. Taylor et.al, in 1959 reported the pyrazine synthesis by condensation of α, β-dicarbonyl and amino malonamidamidine in presence of dilute NH_4OH at 0-20 ^0C [2]. Later, Ohtsuka et. al. in 1979 reported the cyclisation of 2,3-bis (arylidene amino)-3- cyano arylamides followed by oxidation produced corresponding pyrazine [3]. Again, in 1981 E.C. Taylor et.al synthesized pyrazine derivative by reaction of 3,3-dimethoxy-1-(pyrrolidin-1- yl) prop-1-en-2-yl) carbonimidoyl dicyanide and ammonia in MeOH solution [4]. Fukunaga et. al. prepared pyrazine derivative by [4+2] cycloaddition reaction between yn-amines and 1,2-dimethoxyethylene (scheme. IV. A. 5) [5].



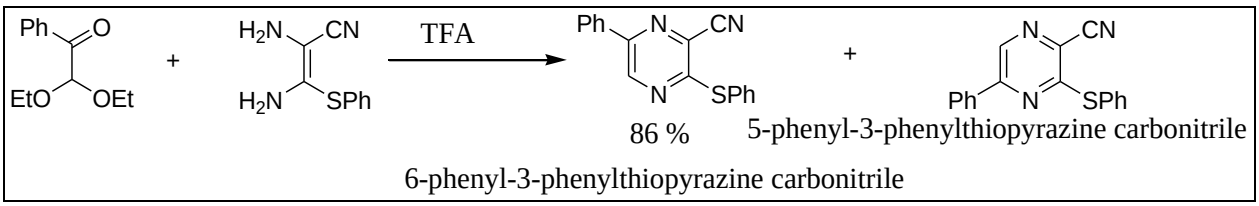
Scheme. IV. A. 5. [4+2] cycloaddition reaction for pyrazine synthesis

Later, Buechi et. al. in 1991 provided the regioselective formation of alkyl pyrazine by the condensation of α-oximido carbonyl and allyl amines [6]. In 1997 T. L. Gilchrist reported the preparation of pyrazine through the formation of dihydro pyrazine followed by oxidation using 1, 2- diaminoethane and 1, 2-dicabonyl (scheme. IV. A. 6) [7].



Scheme. IV. A. 6. Gilchrist pyrazine synthesis

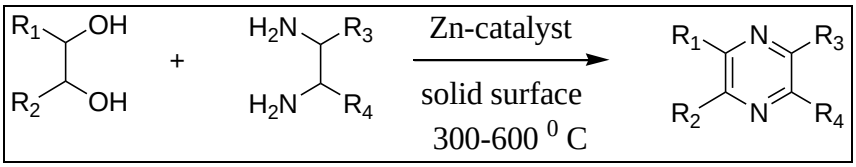
In, 2001 W. Zhang et al. synthesized a pyrazine derivative 6-phenyl-3-phenylthiopyrazine carbonitrile selectively using 2, 3- diamiono-3-phenylthio-acrylonitrile and 2,2-diethoxy acetophenone in excess TFA (scheme. IV. A. 7) [8].



Scheme. IV. A. 7. Selective synthesis of 6-phenyl-3-phenylthiopyrazine carbonitrile

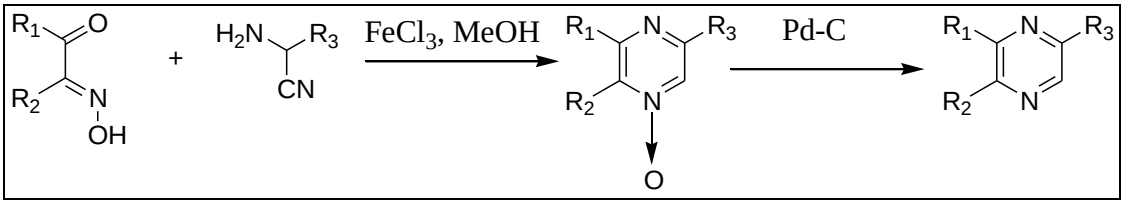
This synthetic approach further continued as a method of options to prepare pyrazine and its derivative among the chemist (e.g. ortho linked oxacalix-[2]-benzene-[2]-pyrazine prepared by L. W. Kong et al) [9].

Besides these metal free catalytic approaches, a number of methods using metal catalyst for pyrazine synthesis are also reported. Such as Anderson et al. in 1967 reported deamination of diethylenetriamine a mixture of catalyst Mo_2O_3: P_2O_5: Al_2O_3 (in ratio 5:1:94) to produced pyrazine derivative [10]. J. Okada in 1974 reported the condensation of diamines with diol in presence of granular alumina in vapour phase for the first time [11]. Sato in 1978 reported pyrazine preparation by reaction of diamine and diol in presence of Zinc catalyst at 300-600 ^{0}C over solid surface such as silica or alumina or silica-alumina (scheme. IV. A. 8) [12].



Scheme. IV. A. 8. Formation of pyrazine using Zn-catalyst

Further, Lee et al. prepared pyrazine using copper-chromite catalyst [13]. In 2002 Itoh et al. reported preparation of pyrazine through the synthesis of pyrazine-N-oxide by reaction of iso-nitroso acetophenone and aminoacetonitrile using $FeCl_3$ as a catalyst followed by subsequent reduction by Pd-C (scheme. IV. A. 9) [14].

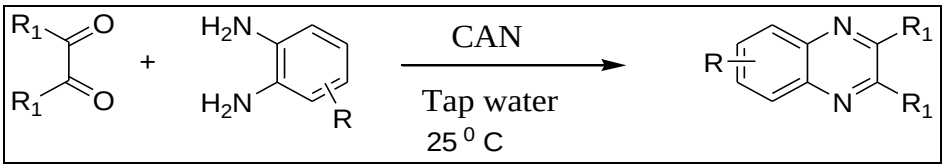


Scheme. IV. A. 9. Itoh et al. process for pyrazine synthesis.

In 2003 Raw et al. reported the reaction of α-hydroxyl ketones and 1,2- diamines in KOH-MeOH using MnO_2 as a catalyst to prepared pyrazine [15]. Later, Park et al. prepared methyl pyrazine by reaction of ethylenediamine and propylene glycol using $CuO\text{-}ZnO\text{-}SiO_2$ as a catalyst [16]. Moreover, Latha et al. reported preparation of pyrazine selectively from ethylenediamine using copper oxide-copper chromite catalyst [17] and also Ghosh et al has reported the greener protocol for pyrazine synthesis [18].

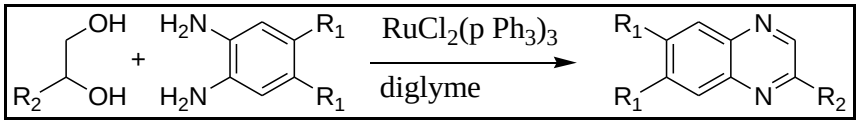
IV. A. 2. 2. 2. Modern method of preparation of quinoxaline:

As the classical method for quinoxaline preparation required strong acidic medium, a more suitable and acceptable method is a basic concern for modern synthetic chemist. Recently literature survey reveals a number of methods for the synthesis using different precursor. Basically, reaction of *vic*-diketo with *vic*-diamines using different catalyst is the most straight forward method (e.g. More et al. recently reported cerium (IV) ammonium nitrate catalysed synthesis of quinoxaline derivative, scheme. IV. A. 10) [19].



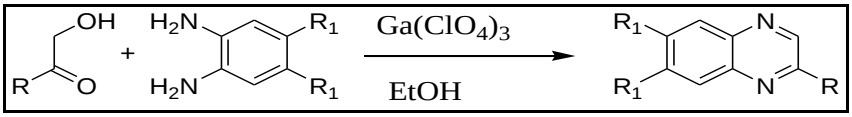
Scheme. IV. A. 10. CAN catalyse quinoxaline synthesis

Again, Esmaeilpour et al. used Fe_3O_4@SiO_2/ Schiff base complex nano particle as their potent catalyst [20] and Brahmachari et al. took magnetically separable $MnFe_2O_4$ as a catalyst [21]. There also certain other precursors are used for quinoxalines synthesis. Such as: *vic*-diol as reported by Cho et al. during their synthesis of quinoxaline by the reaction of substituted *o*-phenylene diamines and *vic*-diols using ruthenium complex as a catalyst; scheme. IV. A. 11). [22]



Scheme. IV. A. 11. Ruthenium catalysed quinoxaline synthesis from *vic*-diol.

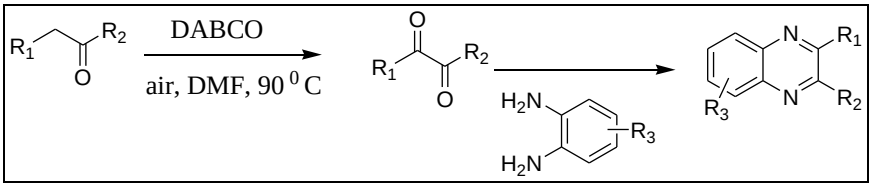
Moreover, α-arylimino oxime (e.g. Xekoukoulotakis et al. reported the cyclisation of α-arylimino oxime in presence of acetic acid under reflux condition for quinoxaline synthesis) [23], α-diazoketones (as reported by Yadav et al. reported cyclisation of α-diazoketones and 1,2-diamine using $Cu(OTf)_2$ as potent catalyst [24]) and α-hydroxy ketones (e.g. Pan et al. synthesized quinoxaline by cycloaddition of α-hydroxy ketones with o-phenylene diamines using $Ga(ClO_4)_3$ as a catalyst, scheme. IV. A. 12 [25]; again, Sithambaram et al. used manganese octahedral molecular sieves as their potent catalyst for the tandem process [26]) are also used as a precursor.



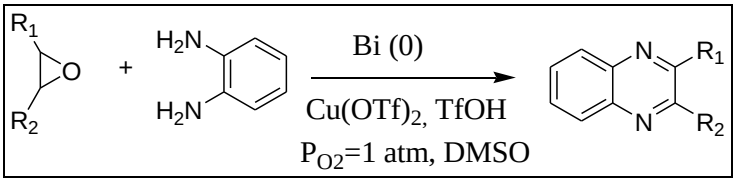
Scheme. IV. A. 12. Quinoxaline synthesis via cyclisation of *α*-hydroxy ketones and *o*-phenylene diamines

Again, deoxy-benzoin (e.g. Qi et al. described the DABCO catalysed in-situ oxidation followed by cyclization of deoxy-benzoin with aryl-1, 2-diamine to quinoxaline, scheme IV. A. 13) [27], epoxide (e.g. Antoniotti et al. gave the Bi(0) catalysed synthesis of quinoxaline from epoxide and

ene- 1,2-di amine using $Cu(OTf)_2$ and TfOH as additive in DMSO solvent, scheme. IV. A. 14) [28], 1,2-Diaza-1,3-butadienes (such as, Aparicio et al. describe the direct synthesis of quinoxaline from 1,2-Diaza-1,3-butadienes by reaction with 1,2-iamines) [29], nitroolefins (e.g. Chen et al. reported quinoxaline synthesis by reaction of nitroolefins with *o*-phenylene diamines using $CuBr_2$ as a catalyst) [30],*o*-alkynyl aldehydes (e.g. Rustagi et al. reported regioselective tandem reaction for quinoxaline synthesis from *o*-alkynyl aldehydes using Ag(I) salt as a catalyst) [31], alkynes (Wnag et al. reported Cu catalysed synthesis of quinoxaline using *o*-phenylene diamines and terminal alkynes in presence of bases) [32], phenacyl bromide (e.g. DABCO catalysed quinoxaline preparation by phenacyl bromide and aryl-1,2-diamine via cyclization-oxidation process) [33] are also used rather than the reactive 1,2-diketo compounds.



Scheme. IV. A. 13. DABCO catalysed oxidation-cyclisation reaction for quinoxaline synthesis.



Scheme. IV. A. 14. Bi (0) catalysed quinoxaline preparation from epoxide.

Other elegant methods comprise with: reaction of 2-nitro aniline with *vic*- diol by hydrogen transfer (e.g. ruthenium catalysed hydrogen transfer technique for quinoxaline synthesis reported by Xie et al.) [34], reaction of polymer linked *o*-Nitrophenyl carbamate with *α*-bromo ketone *via* sequential reductive coupling and cyclisation reported by Singh et al. [35], microwave-irradiation technique (e.g. Zhou et al. reported catalyst free synthesis of quinoxaline derivative by microwave irradiation, [36] and via benzyne intermediate formation on solid phase as reported by Dixon et al.[37] are also been reported with varied success.

IV. A. 3. Conclusion:

Although, variety of methods are available for the synthesis of both pyrazine and quinoxaline, most of them are limited by harsh reaction condition, long reaction time, tedious work-up procedure, use of toxic solvent or heavy metal catalyst and also for poor yield. These drawbacks motivate the author of this thesis for the development of a milder, efficient and environmentally being method for their synthesis pyrazine and quinoxaline moieties.