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Review On "Synthesis Of Pyrazine;Imidazolidine-2,4-Dione And Pyrimidines And Its Derivatives"

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ABSTRACT:
Pyrazine; Imidazolidine-2,4-dione and Pyrimidines are an example of aromatic heterocyclic organic compound. It is a monocyclic compound. They can be obtained naturally or it can be synthesized in laboratory. Pyrazine; Imidazolidine-2,4-dione and Pyrimidines and its derivatives play an important role in the medicinal chemistry and drug discovery with many pharmacological activities. Substitution of various chemicals on Pyrazine; Imidazolidine-2,4-dione and Pyrimidines nucleus gives important synthetic product and strategy in the drug discovery process. These derivatives contain versatile nitrogen containing heterocyclic compounds. These heterocylic compounds and its derivatives were used as building blocks for the important therapeutic compounds in medicine. Their nucleus plays a very important role as a therapeutic agent.They exhibit pharmacological activities such as antimicrobial, antiviral, anticancer, antiinflammatory, analgesic activity,anti-ulcer, anti-diabetic activity etc. Their nucleus gives active sites for the reaction like 2 and 5 position which gives potent therapeutic agents. The main aim of review is to help medicinal chemists for the development of SAR on Pyrazine; Imidazolidine-2,4-dione and Pyrimidines for each activity and to review the work reported, chemistry and pharmacological activities of Pyrazine; Imidazolidine-2,4-dione and Pyrimidines derivatives during past years. The major aim for this article is review on Pyrazine and Pyrimidines synthesis and the biological activity. Pyrazine as a heterocylic compound was commonly found in plants, animals, insects, marine organisms and microorganisms. Pyrazine, Pyrimidines anditsderivativeswere commonly used inindustriesmainly forflavorandpharmaceuticalapplications.

KEYWORDS: *Pyrazine; Pyrimidines; Biginelli reaction; HMDS; DMF*

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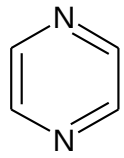
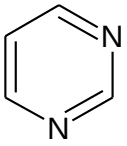
I. INTRODUCTION

The chemistry of heterocyclic compounds (N, S, and O containing compounds)is important for the discovery of some novel drugs. Amino acids, alkaloids, vitamins, hormones, hemoglobin, and many synthetic drugs and dyes contain heterocyclic ring systems[1-3]. There are large numbers of synthetic heterocyclic compounds like pyrimidines, Pyrrole, pyrrolidine, furan, thiophene, piperidine, pyridine, Imidazolidine, imidazole and thiazole and they gives significant biological activity. Among these Pyrimidines, Imidazolidine and Pyrazine are of great interest[4-6].The discovery of pyrimidines by the scientist Scheele; he isolated uric acid in 1776, fused pyrimidine chemistry started. Pyrimidine and Pyrazineare a six membered heterocyclic ring with two nitrogen (N) atoms in their ring. It is a colorless compound, having molecular formula of $C_4H_4N_2$ and molecular weight of 80 Dalton having melting point 22.5^oC and boiling point 124^oC[7-9]. Pyrimidine and Pyrazine is a weaker base than Pyridine. Only one of the nitrogen atoms of the Pyrimidine and Pyrazine can be alkylated by alkylating agents[10], but with tri ethyl oxoniumboro fluoride both nitrogen atoms can be alkylated. Pyrazine is commonly known as 1, 4- diazine. It has 6 membered heterocyclic compounds with two nitrogen atoms in *para* position. It having 6π- electron-deficient and resembles in planar configuration. Pyrimidine and Pyrazine both

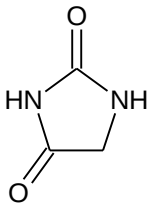
exhibits inductive resonance properties[11]. This is due to the electron withdrawingeffect of nitrogen atoms that is positioned at *para* position (Sato, 2014)[12]. The specific dissociation constantforPyrazinearep*K*a1=0.65and*p*Ka2=-5.78 (Dolezal & Zitko, 2015). The structure of Pyrimidine and Pyrazine are given below ;(Fig no.1)



pyrazine

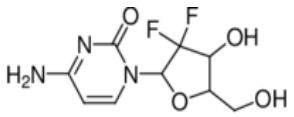


pyrimidine

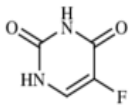


imidazolidine-2,4-dione

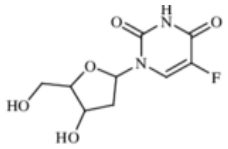
Hydantoin nucleus is an imidazolidine-2,4-dione. Phenytoin drug contain Imidazolidine-2,4-dione heterocylic structure. This drug is anti-epileptic and also known as anticonvulsants. It works by slowing down impulses in the brain that cause seizures. Phenytoin is used to control seizures. It does not treat all types of seizures. The combination of Phenobarbital and phenytoin was recommended for many years for treatment of epilepsy in humans. This combination does not work long time because; side effect of this combination is more. It take about 7 to 10 days for the level of phenytoin in patient body to stabilize on a normal starting dose. It exerts a beneficial effect by reducing seizures only during the first week after severe head injury.[2]. There are various drugs in the market containing Pyrimidine nucleus. Some example of Pyrimidine nucleus drug was given below; (Fig no.2)



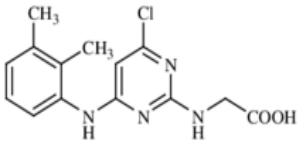
Gemcitabine
(Anti cancer)



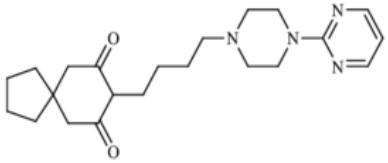
5-Fluorouracil
(Anti cancer)



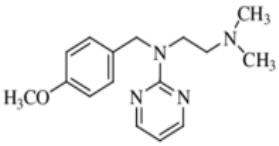
Floxuridine
(Anti cancer)



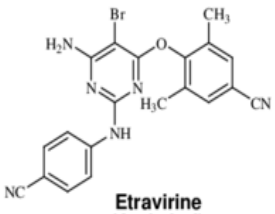
Aronixil
(Anti-hyperlipidemic)



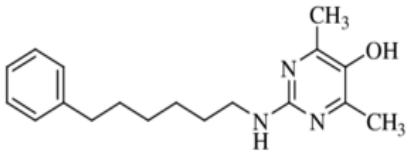
Buspirone
(Anti psycotic)



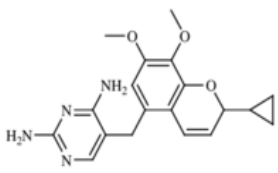
Thonzylamine
(Anti histaminic)



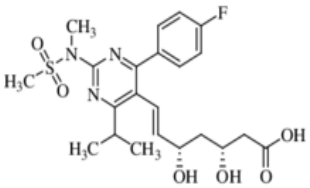
Etravirine
(Anti viral)



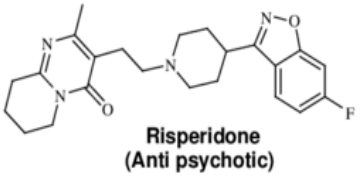
Enazadrem
(Anti psoriatic)



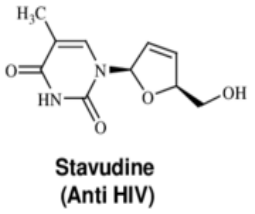
Iclaprim
(Antibiotic)



Rosuvastatin
(Anti lipidemic)

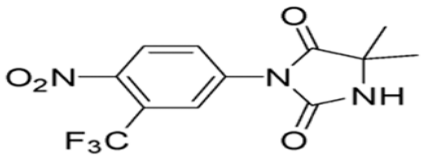


Risperidone
(Anti psychotic)

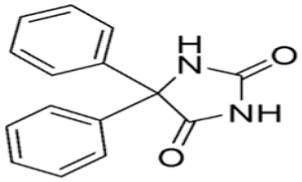


Stavudine
(Anti HIV)

Some example of Pyrimidine nucleus drug was given below ;(Fig no.3)

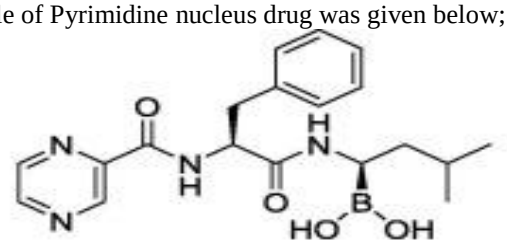


Nilutamide
(Androgen receptor antagonist)

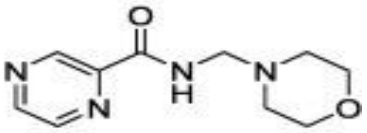


Phenytoin
(Anticonvulsant)

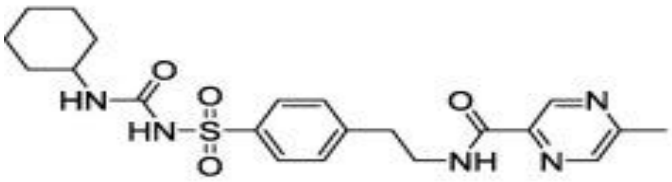
Some example of Pyrimidine nucleus drug was given below; (Fig no.4)



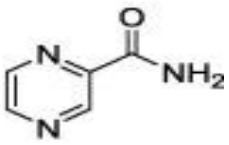
Bortezomib



Morinamide



Glipizide

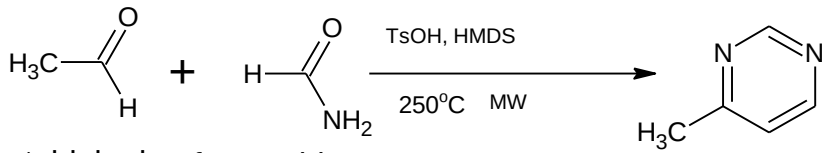


Pyrazinamide

Synthesis of Pyrimidines and Pyrazine:

A) Synthesis of Pyrimidines:

A simple, high yielding synthesis of pyrimidines from aldehyde functional group like acetaldehyde in the presence of HMDS and amide functional group like formamide is reported Under microwaveirradiation[12]**(Scheme 1)**

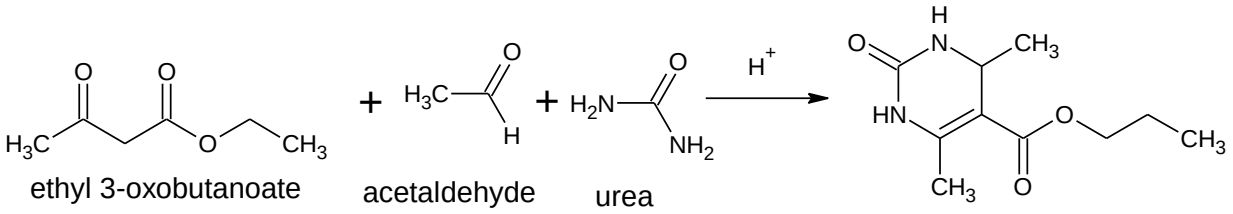


acetaldehyde formamide

4-methylpyrimidine

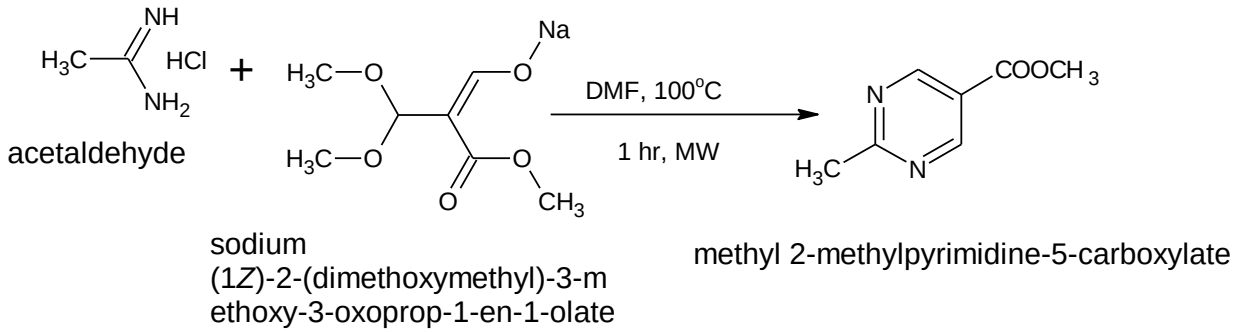
Scheme 1

High yielding synthesis of pyrimidines from ester functional group likesethyl 3-oxobutanoate and aldehyde like Acetaldehyde in the presesnce of urea then it gives propyl 4,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate. It is Most widely used technique for pyrimidine synthesis is that of Biginelli reaction[13] (**Scheme 2)**



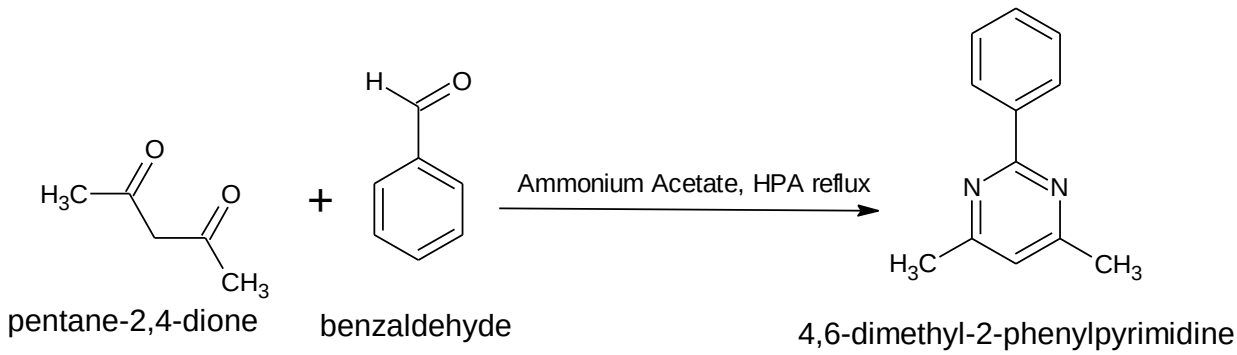
Scheme 2

A method for the synthesis of 2-substituted pyrimidine-5-carboxylic esters or methyl 2-methylpyrimidine-5-carboxylate is described in this approach. The sodium salt of 3,3-dimethoxy-2-methoxycarbonylpropen-1-ol / sodium (1*Z*)-2-(dimethoxymethyl)-3-methoxy-3-oxoprop-1-en-1-olate has been found to react with a variety of aldehyde group in the presences of DMF, 100^{o}C[14]**(Scheme 3)**



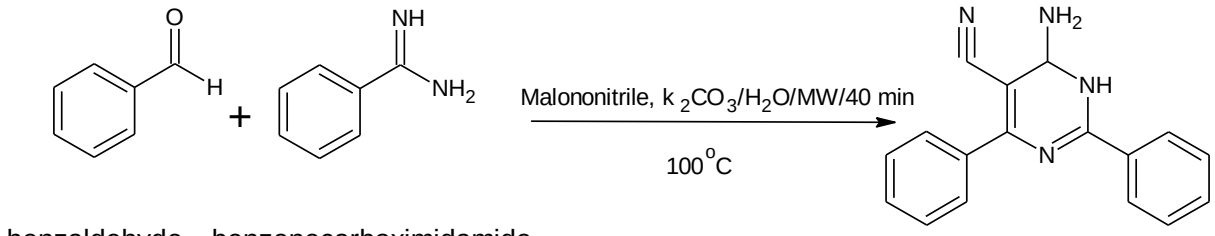
Scheme 3

Pyrimidines was synthesized via a direct oxidative one-pot, three-component, reaction between 1,3- diketone like pentane 2,4-dione, benzaldehyde, and ammonium acetate in the presence of catalytic amounts HPA under reflux in good yields[15].**(Scheme 4)**



Scheme 4

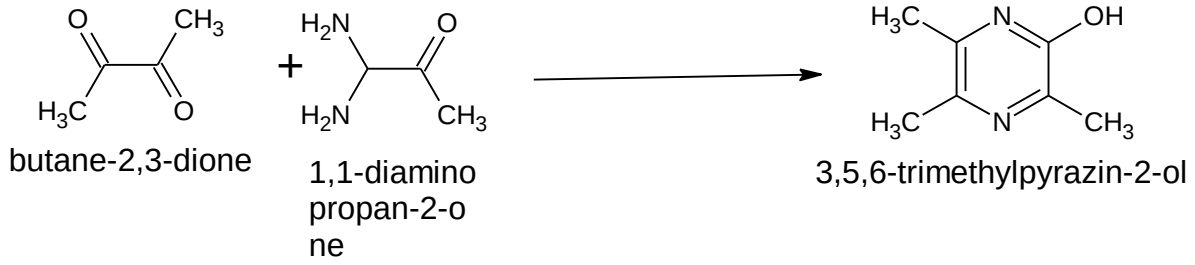
Xavier et al (2013)[28] reported multicomponent microwave assisted synthesis of pyrimidine derivatives. It was reported that aldehyde functional group like Benzaldehyde react with benzene carboximidamide under the condition of Malononitrile, K2CO3 and water MW 40 min then it gives 6-amino-2,4-diphenyl-1,6-dihydropyrimidine-5-carbonitrile[16]. **(Scheme 5)**



Scheme 5

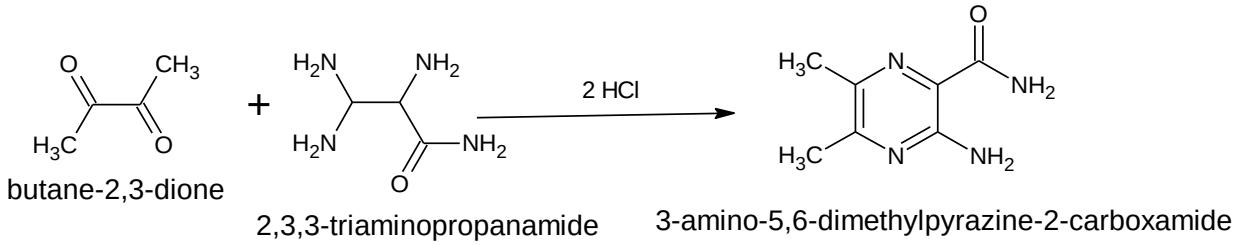
B) Synthesis of Pyrazine:

Inyear1949,JonesdiscoveredthePyrazinederivatives like 3,5,6-trimethylpyrazin-2-ol synthesispathwaythatinvolvedcondensation of α-amino acid amides like1,1-diaminopropan-2-one and 1,2-dicarbonyl butane-2,3-dione. Jones (1949) concludedthatthereactionpathwaywasmoredirect,convenientandhigheryieldcanbeeasilyisolated[17]. **(Scheme 6)**



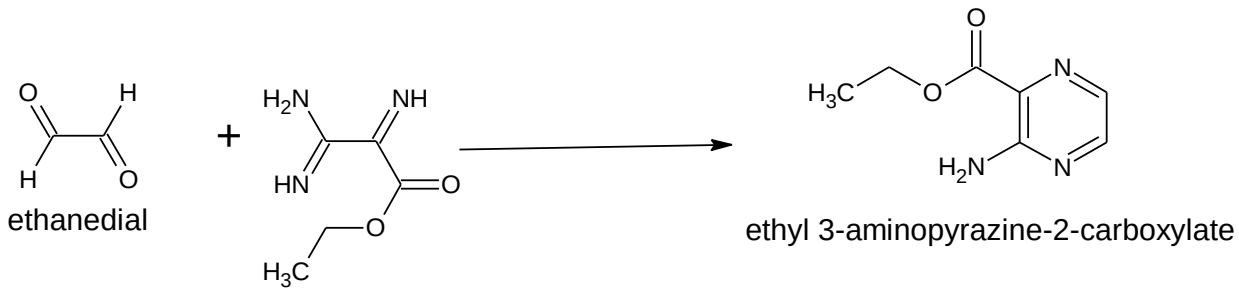
Scheme 6

Ten years later, Vogl and Taylor (1959)reportedthereactionbetweenα,β-dicarbonylbutane-2,3-dione and2,3,3-triaminopropanamide could be used to access Pyrazinederivative at0-20°Cgave76%of3-amino-5,6-dimethylpyrazine-2-carboxamide[18]**(Scheme 7).**



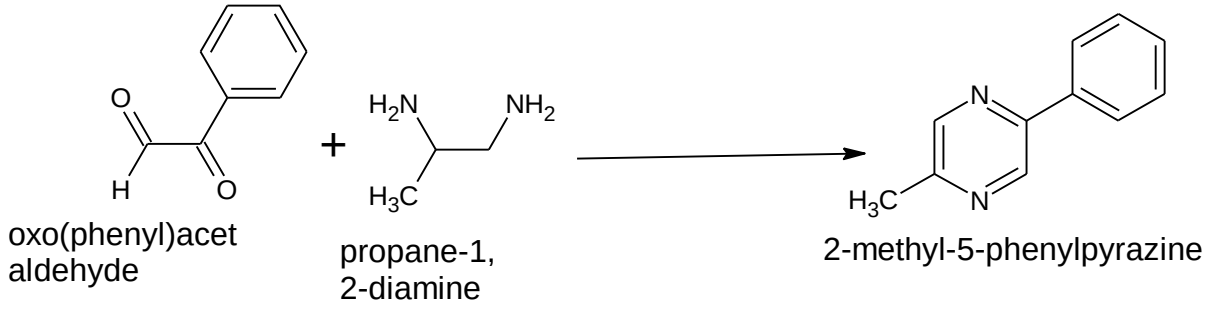
Scheme 7

A couple of years later, Keir *et al.* (1978)reportedthecondensationof1,2-dicarbonyl like ethanedialwithethyl-2-amidino-2-aminoacetatedihydrochloride or ethyl 3-amino-2,3-diiminopropanoateto yieldPyrazine derivatives like ethyl 3-aminopyrazine-2-carboxylate**(Scheme8).**



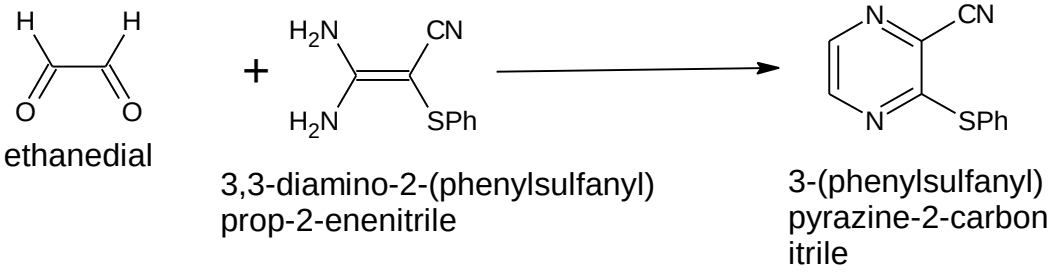
Scheme 8

Ohta *et al.* (1979) reported the condensationofoxo(phenyl)acetaldehyde withpropane-1,2-diaminefollowed by dehydrogenation in the presence ofsodium hydroxide to give a mixture of 2-methyl-5-phenylpyrazine[19] **(Scheme 9).**



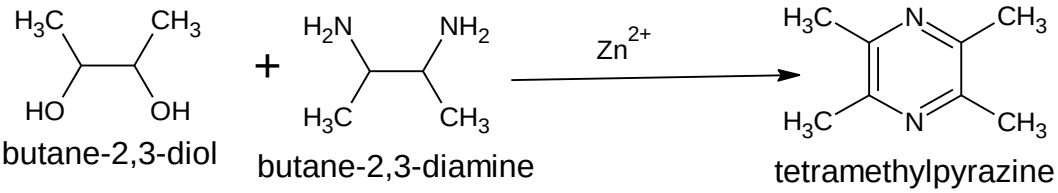
Scheme 9

In 1994, Tazaki *et al.* patented a reactionpathway whereby ethanedial condensed with 3,3-diamino-2-(phenylsulfanyl)prop-2-enenitrile togive3-(phenylsulfanyl)pyrazine-2-carbonitrile **(Scheme10).**



Scheme 10

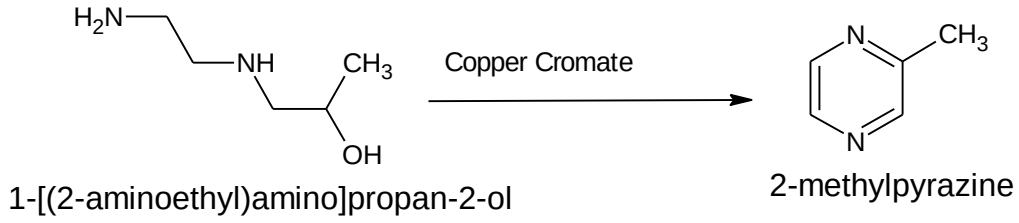
SatopatentedthereactionpathwaytosynthesizePyrazineinthepresenceofzinc(U.S.PatentNo.4,097,478,1978). In this reaction diamine like butane-2,3-diamine and diol likebutane-2,3-diol inthepresenceofzincasthecatalystthroughgasphasecontactreactionat300-600°Cbyutilizingsilica and alumina it gives tetramethyl Pyrazine[20] **(Scheme11).**



Scheme 11

In 1990, Lee *et al.* patented the synthesis ofPyrazineusingcopper-chromatecatalyst(U.S. PatentNo.4,966,970,1990). In this reaction; 1-[(2-aminoethyl) amino] propan-2-ol react with copper-

chromatecatalyst it gives 90% ofyields of 2-methylpyrazine[21]**(Scheme 12).**



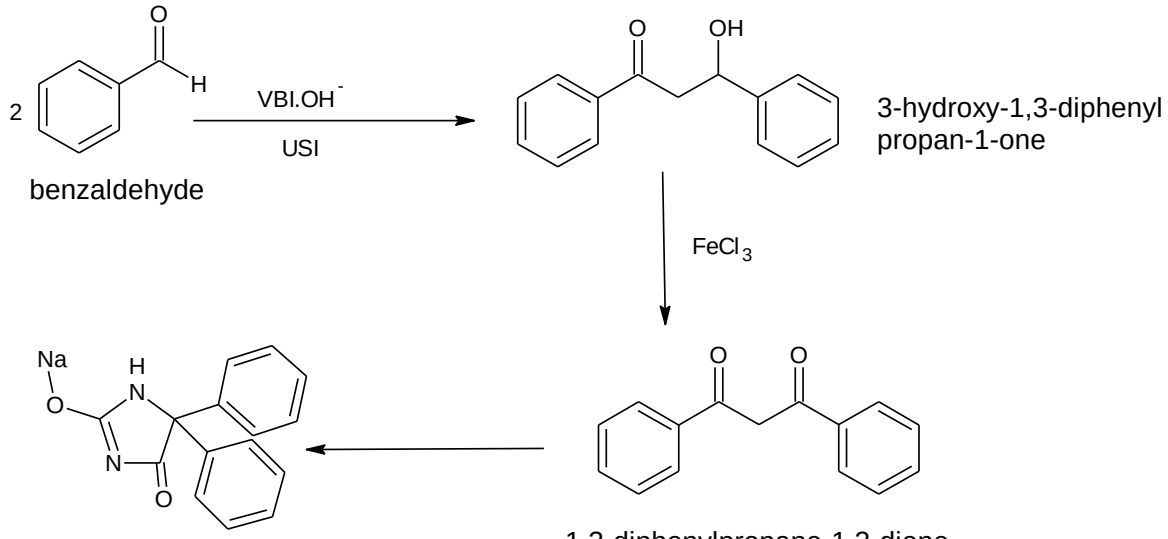
1-[(2-aminoethyl)amino]propan-2-ol

2-methylpyrazine

Scheme 12

C) Synthesis of Imidazolidine-2,4-dione:

Benzaldehyde was used as a raw material through the condensation. Benzaldehyde was reacted with benzoin condensation, oxidation asnd Cyclization reaction to gives a phenytoin sodium product under the supersonic wave radiation. Vitamin B1 used as catalyst in the Styrax condensation reaction and Fecl3.6H2O used as oxidant and concentrated nitric acid[12]**(Scheme 13).**



benzaldehyde

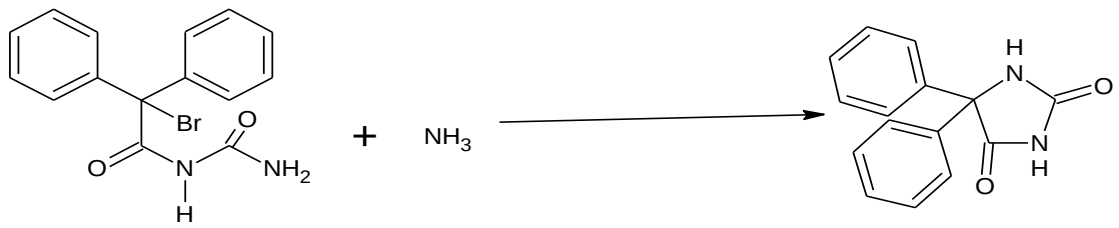
3-hydroxy-1,3-diphenyl propan-1-one

1,3-diphenylpropane-1,3-dione

sodium 4-oxo-5,5-diphenyl-4,5-dihydro-1*H*-imidaz ol-2-olate

(Scheme 13)

In 1996, Leevisd *et al.* patented the 2-bromo-N-carbamoyl-2,2-diphenylacetamide react with alcoholic ammonia to gives a phenytoin[13]**(Scheme 14).**

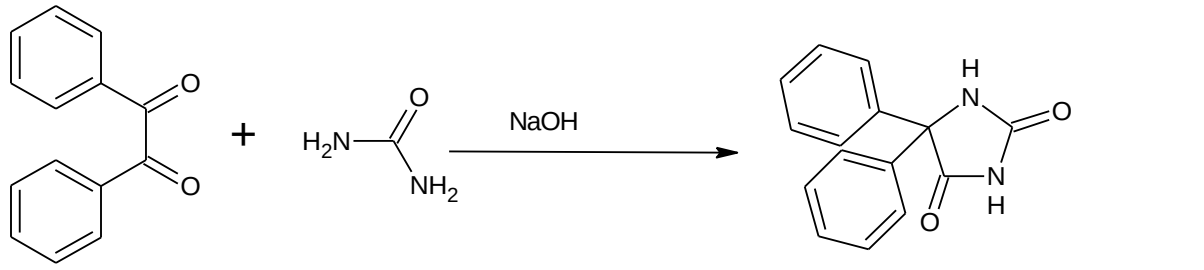


2-bromo-*N*-carbamoyl-2,2-diphenylacetamide

Phenytoin

(Scheme 14)

In 2005, Pitter *et al.* patented the 1,2-diphenylethane-1,2-dione react with urea in presence of base catalyst sodium hydroxide and ethanol to gives 5,5-diphenylimidazolidine-2,4-dione[14]**(Scheme 15).**



1,2-diphenylethane-1,2-dione

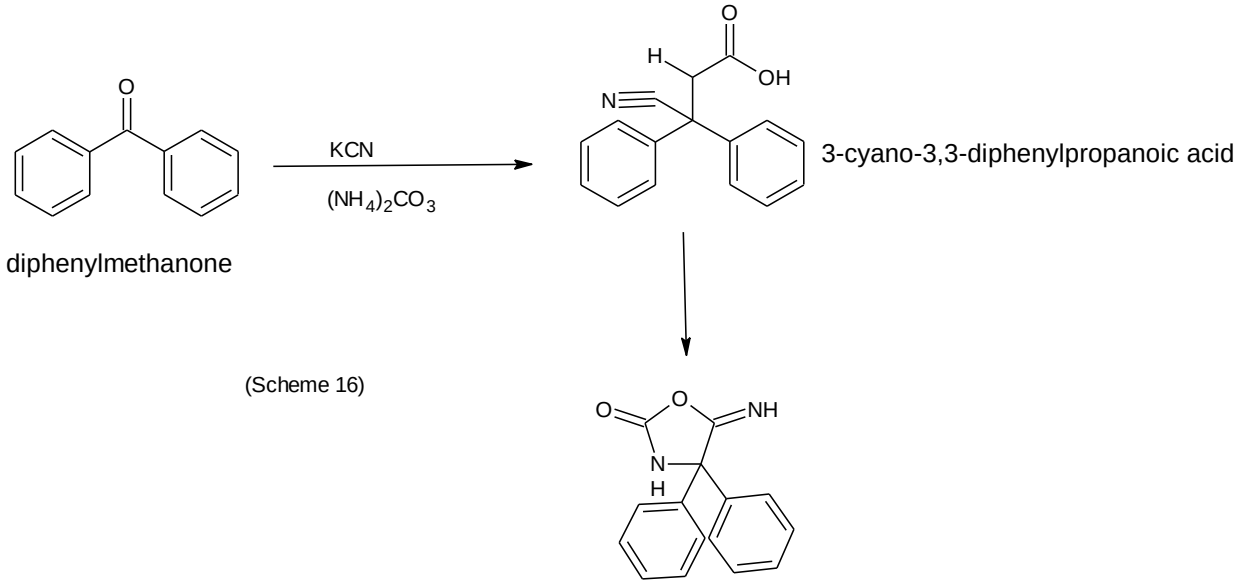
Benzil

5,5-diphenylimidazolidine-2,4-dione

Phenytoin

(Scheme 15)

In 1946, H. R. Henze and parke-Davis *et al* are prepared of phenytoin from Benzophenone. In reaction diphenyl methanone react with potassium cyanide and ammonium carbonate in 60% ethanol to gives phenytoin. It can also prepared by reacting, Benzophenone, sodium cyanide and ammonium bicarbonate[15] **(Scheme 16).**



diphenylmethanone

(Scheme 16)

5-imino-4,4-diphenyl-1,3-oxazolidin-2-one

II. CONCLUSION:

Alltechniquesdescribedin this reviewcanbeconsidered to prepare Pyrimidines, Imidazolidine-2,4-dione and Pyrazine and variety ofPyrimidines and Pyrazine derivatives.Differentsyntheticapproachescanbeusedfordifferentsubstituentsthatareattachedtothe Pyrimidines, Imidazolidine-2,4-dione and Pyrazinering.Amongallofthereviewedapproaches,Pyrazine, pyrimidines anditsderivativeswere commonly used inindustriesmainly forflavorandpharmaceuticalapplications. Pyrimidines,Imidazolidine-2,4-dione and Pyrazine derivatives are well known for their medicinal properties due to the presence of pyrimidine base in thymine, cytosine and uracil, which form the building blocks of DNA and RNA.

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