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Synthesis of Benzimidazoles using High Yield Thermal Method

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Abstract

Benzimidazoles and their derivatives represent an essential class of bioactive molecules. Benzimidazole derivatives hold mechanical, biochemical, and pharmaceutical significance, and they can also serve as ligands for transition metals.Benzimidazole derivatives are known to exhibit a wide range of biological activities and can be synthesized using various solvents and ring-closing reagents.

The present review focuses on the comparative synthesis of benzimidazole derivatives using both microwave and thermal methods. It has been observed that the microwave and thermal methods of synthesizing benzimidazoles and their derivatives offer several advantages, including increased yield (up to 10% to 50%) and significantly reduced reaction time (reduced by 96% to 98%) compared to conventional synthesis methods.

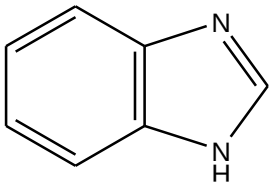
The synthesized compounds are subjected to in vitro antibacterial and antifungal activity evaluations. Additionally, it has been observed that certain compounds exhibit remarkable anticancer activity.

Keywords: Benzimidazoles, Thermal Synthesis, High Yielding methods

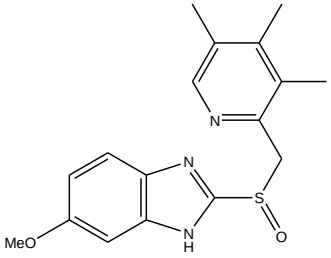
INTRODUCTION-

Benzimidazole and derivatives of benzimidazole are important natural and synthetic nitrogen containing 5- memberedheterocyclic aromatic compound consist of benzene ring fused with imidazole ring**[1]**. Due to the wide range of pharmacological activities and industrial accompanying with synthetic applications associated with benzimidazole and its derivatives, several methods for their synthesis have been reported**[2]**. Benzimidazole derivatives have occupied a prominent place in medicinal chemistry because of their significant properties as therapeutics in clinical applications. The most prominent benzimidazole compound in nature is N-ribosyl-dimethyl benzimidazole, which serves as an axial ligand for cobalt in Vitamin-B_{12}**[3]**. Furthermore, these heterocyclic compounds can be extensively used as ligands for transition metals**[4]**. Benzimidazole is a versatile pharmacophore reducing a diverse range of biological activities including anti-cancer, anti-ulcer, analgesics (opioids, cannabinoids), anti-pasmodic, anti-microbial activity against Escherichia coli (Gram-negative bacteria), Staphylococcus aureus (Gram-positive bacteria), Candida albicans (fungal stain), pesticide, anthelmintic, anti-inflammatory,anti-fungal, anti-viral and it acts against some viruses such as HIV and herpes (HSV-1)**[5]**Also, it is an

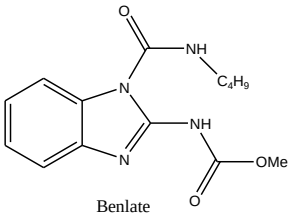
inhibitor of chemokine receptor (CXCR3)**[6]** and lymphocyte tyrosine kinase (LCK)and it also blocks DNA replication. The synthesis of benzimidazole can be accomplished through various methods, with one of the most convenient approaches involving the condensation of o-phenylenediamines with cyclizing agents like aldehydes, formic acid, or their derivatives**[7]**. Moreover, the enhancement of benzimidazole's activities can be achieved through various modifications**[8].**



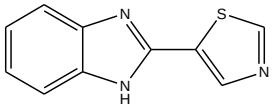
Various potent drugs based on their structures formed by benzimidazole derivatives are now being currently practiced in the market, like albendazole, omeprazole, thiabendazole, benlate,galeterone, dimethyl benzimidazole, liarozole, 5,6-Dichloro-1-B-d-ribofuranosyl benzimidazole, DB921, etc. On seeing the importance and continuation for our project work on benzimidazole derivatives, it was felt worthwhile to synthesize benzimidazole derivatives and screen them for analgesic and anti-inflammatory activities**[9].**



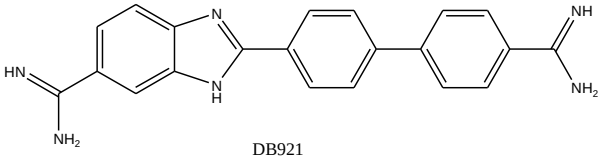
Omeprazole



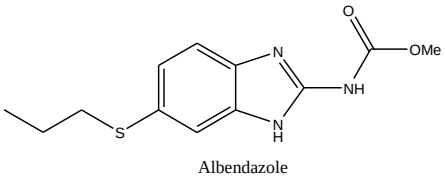
Benlate



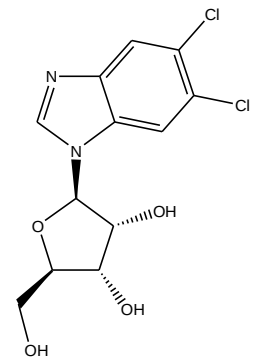
Thiabendazole



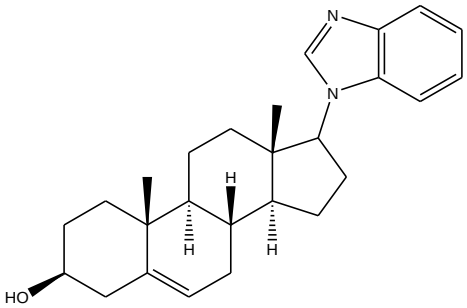
DB921



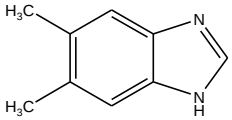
Albendazole



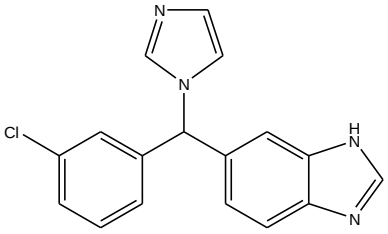
5,6- Dichloro-1-β-d-ribofuranosyl benzimidazole



Galeterone

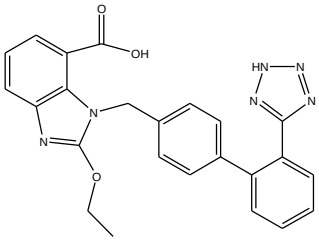


Dimethybenzimidazole

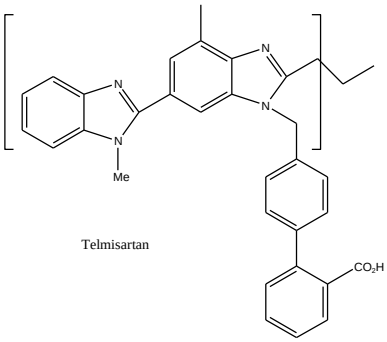


Liarozole

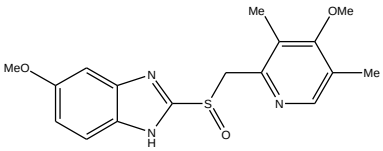
The substituted benzimidazole have been reported as valuable bioactive structures, such as specific angiotension II receptor type 1 selective antagonists, for example, the antertensive marketed under trade names Atacand (canadesartan) and Micardis (telmisartan) potent inhibitors of Parietal cell proton pump, the H+/K+ATPase, exampleantiulcer with trade name Nexium (esmeprazole), a proton pump inhibitor used to treat peptic ulcer and gastro esophageal reflux diseases**[10].**



Candesartan



Telmisartan



Esomeprazole

Undoubtedly, benzimidazoles are important scaffolds. Hence, substantial efforts have been made to search for new synthetic strategies that would provide access to chemical space currently unattainable by existing methods and would hold significant importance in synthetic chemistry.

However, methods to prepare substituted benzimidazoles have tremendously increased during the last few years.

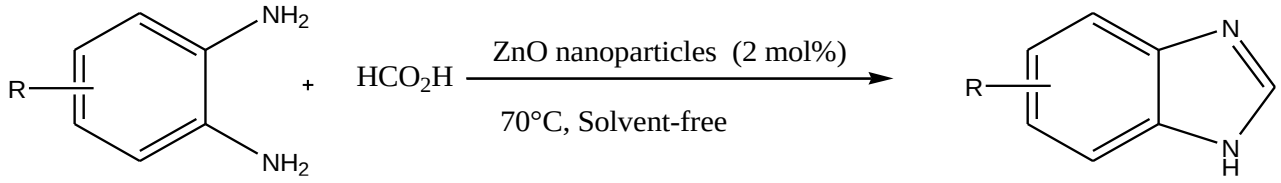
Strengthening of o-aminobenzenethiol, o-aminophenol, or o-phenylenediamine with acid chlorides, carboxylic acids, esters, aldehydes, nitrile oxide, dibromomethylarenes, and ortho esters in the presence of a strong acid is one of the methods that has been used for the synthesis of these derivatives.

But we will focus on the methods of synthesis of benzimidazoles at high temperature or by using microwave and thermal radiation.

SYNTHESIS OF BENZIMIDAZOLES-

1) Zinc- oxide nanoparticles (NAP-ZnO) are certainly some of the most interesting multifunctional metal oxides, because they have surface properties that suggest that a very rich organic chemistry may occur there. So far, a variety of techniques have been employed in the preparation of nanocrystalline ZnO with different particle morphologies and sizes. However, most of these methods require a strictly controlled synthesis environment, expensive equipment, and intricate procedure**[1,11].**

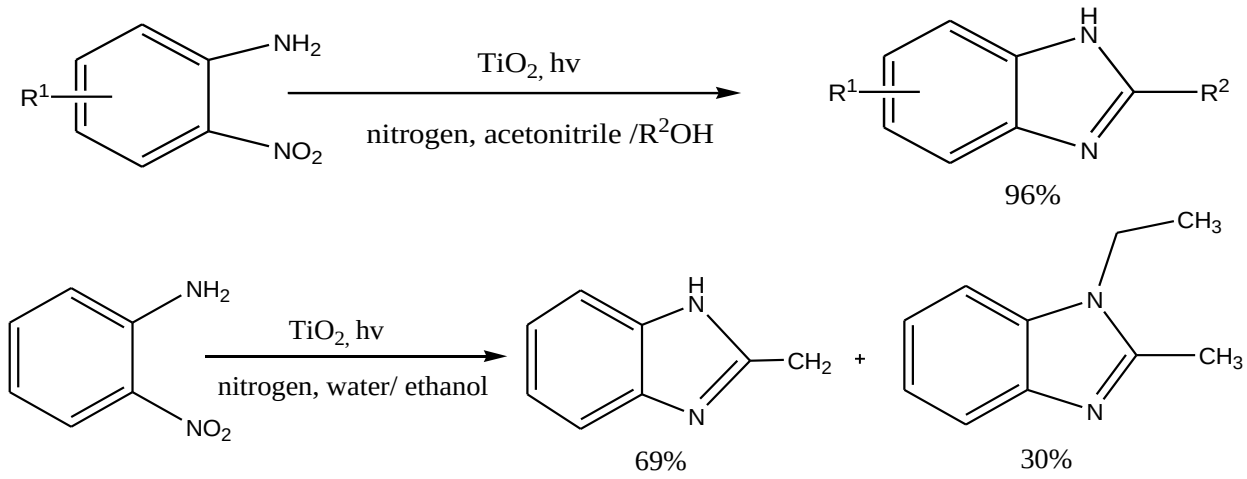
Herein, we report the conversion of formic acid to benzimidazoles in the presence of NAP-ZnO selectively and effectively by mechanochemical processing.**[1,11]**(Scheme.1)



Scheme.1

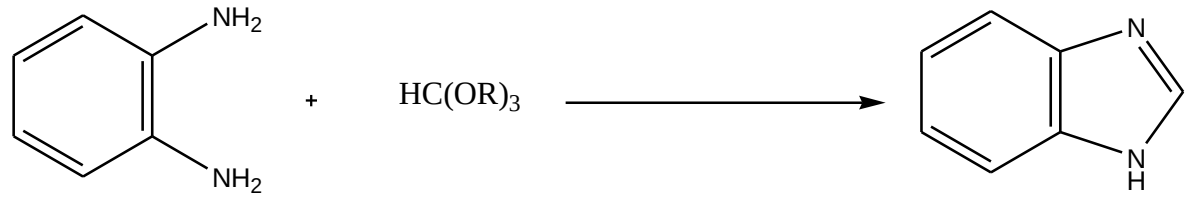
2)TiO_2 induced conversion of o-dinitrobenzene in nitrogen-saturated ethanol with ultraviolet (UV) light resulted in the formation of 2-alkylbenzimidazole. Here we study about the photocatalytic activity of TiO_2 in the conversion of dinitrobenzene and substituted dinitrobenzene in ethanol and 1-propanol**[12].**

Herein, synthesis and mechanism steps taken to validate the reaction are given. (Scheme.2)



Scheme.2

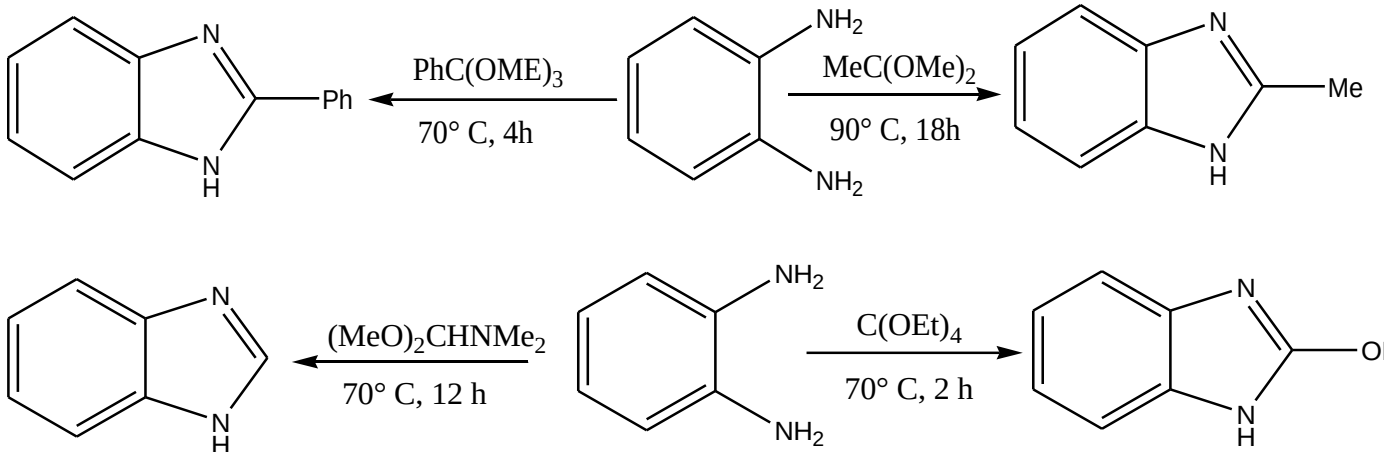
3)The reaction of o-phenylenediamine with selected esters was studied here. Thus, treatment of 1a with tetraethyl orthocarbonate and N, N-dimethylformamide dimethyl acetal (DMFDMA) afforded 2-ethoxy-H-benzimidazole (4a) and 2a in 93% and 86% yields respectively**[13].**(Scheme.3)



R= OMe or OEt

Scheme.3

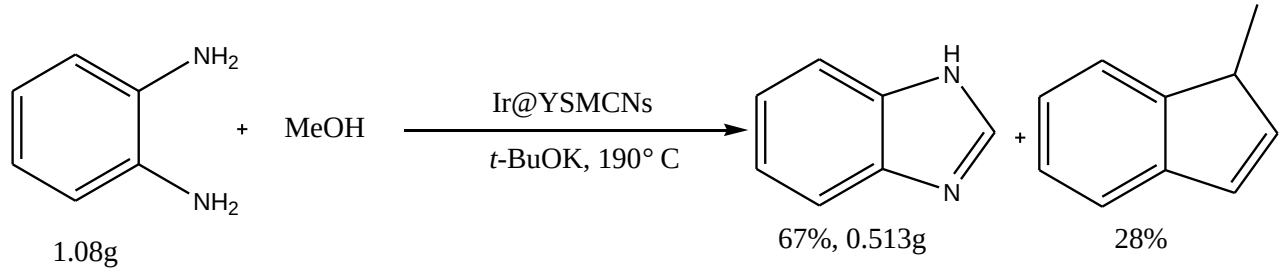
Treatment of 1a with trimethyl orthobenzoate under solvent free conditions at 70°C for 4 hours gives 5a in 90% yield but the same reaction of 1a with trimethyl orthoacetate failed to give any product at 70°C for 24 hours; the same reaction proceeded smoothly under solvent free conditions at 90°C for 18 hours gave 6a in 87%**[13].** (Scheme.4)



Scheme.4

4)Synthesis of benzimidazole and N-methyl benzimidazole from o-phenylenediamine and methanol catalyzed by Ir@YSMCNs. Reaction conditions:

-- o-phenylenediamine (1.010 g, 5 mmol), t-BuOK (0.560 g, 5 mmol), methanol (15 mL),Ir@YSMCNs (0.125 g, 4 wt.% Ir content) for 30 hours.Following synthesis is given below: **[14]** (Scheme.5)



1.08g

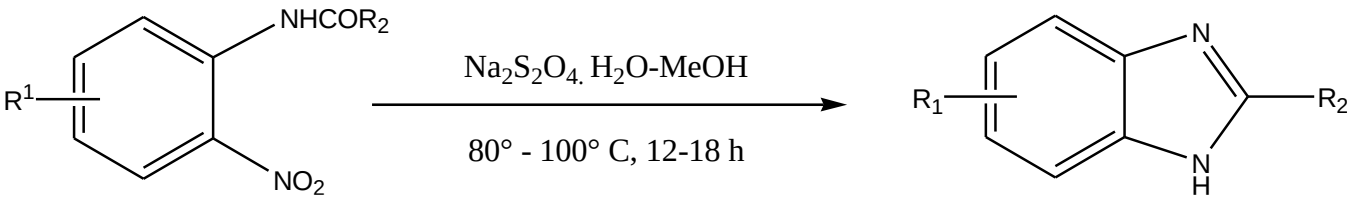
67%, 0.513g

28%

Scheme.5

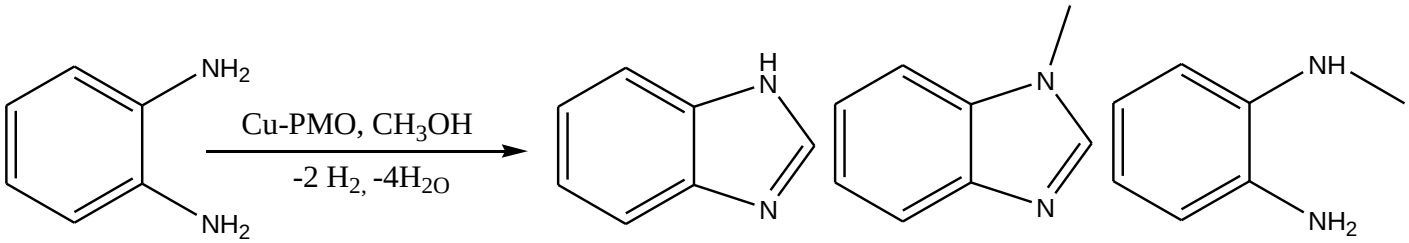
5)Benzimidazole formation from o-nitro anilides, we could detect and o-amino sulphonic anilide and isolate o-amino anilide before formation of benzimidazoles. The results indicated that when a solution of o-nitroanilide in water was treated with 3.5 equivalents of solid sodium dithionite at 80°C, followed by

an increase in the reaction temperature to 100°C, the formation of 2-substituted benzimidazole derivatives occurred in a straightforward manner through reductive cyclo-dehydration within 12-18 hour. (Scheme.6)



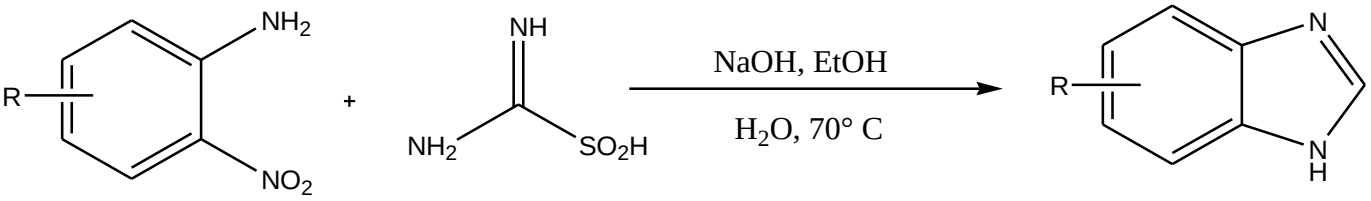
Scheme.6

6)There are various methods of preparation of benzimidazoles. One of them is an additive-free method from various 1,2-diaminobenzenes by heating them in the starting material scMeOH, that acts as both solvent and a reactant, in the presence of Cu-PMOs**[15]**.(Scheme.7)



Scheme 7. 1,2-diaminobenzene is heated in scMeOH by using Cu-PMOs gives Benzimidazole(1a) and N-methyl benzimidazole(1b).

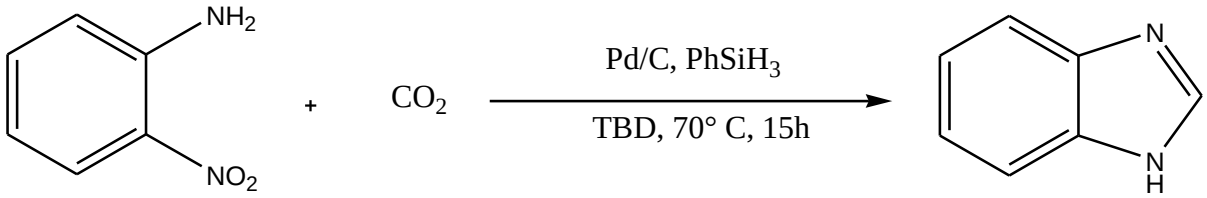
7)Benzimidazoles can be prepared from 2-nitroanilines and thiourea dioxide (TUD)by heating at 70 °C in mixed solvent of H_2O and EtOH (in ratio v/v, 3/1).Thiourea dioxide (20 mmol) is added in batches in a solution of substituted 2-nitroanilines (5 mmol) and NaOH (20mmol) in 15 mL H_2O. The mixture is stirred to the timewhich is to be required to complete the reaction. Then after cooling down of the mixture, 10% NaOH is added until pH=9-10, then wash out the filtered solid by water and crude product is obtained. Recrystallization of crude product happens from water which gives a white solid **[16]**(Scheme.8)



Scheme 8. Synthesis of benzimidazole by 2-nitroanilines and TUD in presence of NaOH in EtOH/H_2O at 70 °C.

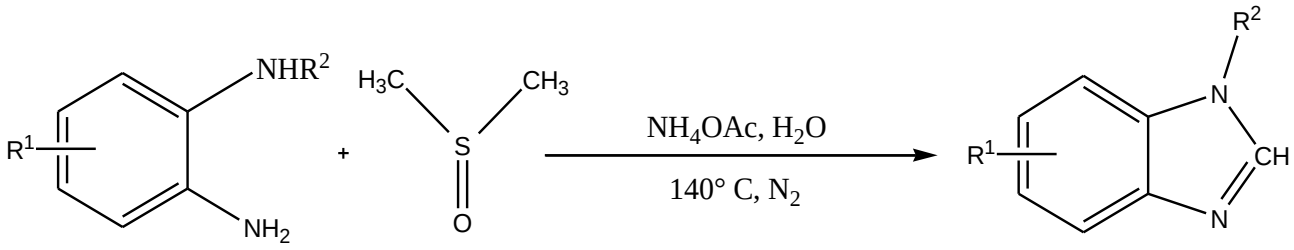
8)Recent studies from 2021 have shown a more efficient and sustainable method for synthesizing benzimidazole directly from o-nitroaniline. This method utilizes phenyl silane as the reductant, acetonitrile as the solvent, and atmospheric CO2 at a temperature of 70°C for approximately 15 hours.

Among the various palladium catalysts tested, Pd/C yielded the highest yield, and in the case of silanes, both PhSiH3 and PMHS provided the highest yields**[17].**(Scheme.9)



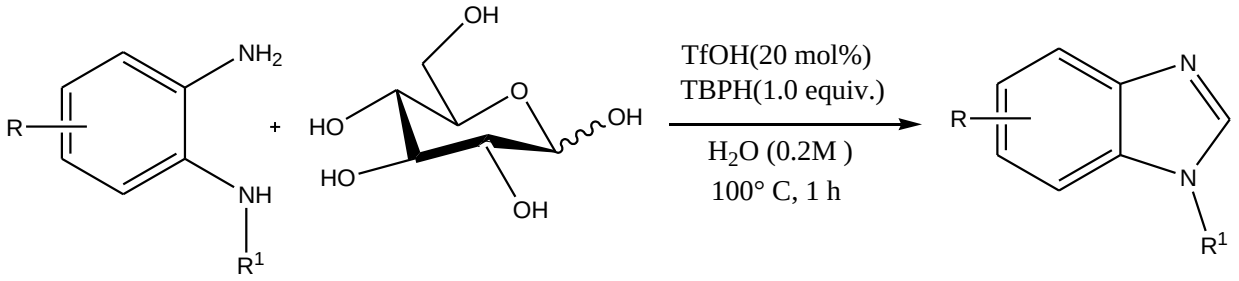
Scheme 9. Synthesis of benzimidazole from o-nitroaniline

9)Also, if o-phenylenediamines(0.2 mmol) are treated with NH_4OAc (6 equiv), H_2O (80 µL) and 2Ml DMSO at 140 °C, it gives 2-unsubstituted benzimidazolesas product in 35-86% yields**[18].**(Scheme.10)



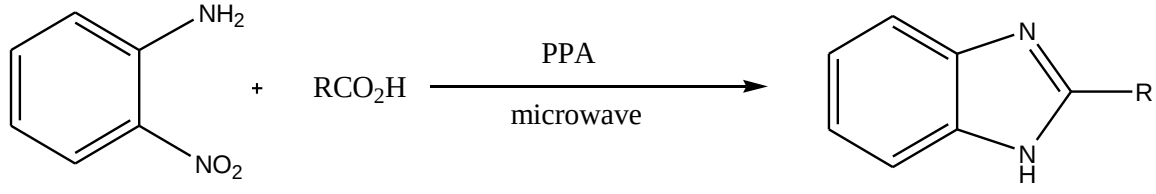
Scheme 10. Synthesis of 2-unsubstituted benzimidazole from o-phenylenediamine

10) On using o-phenylenediamine (1.0 mmol), D glucose (1.0 equiv) and tert-butyl hydroperoxide (70%, 1.0 mmol), TfOH (0.2 mmol) and 0.02 M water stir at 100 °C for about 1 hour gives 1-H-benzo[d]imidazole in 35% of yield**[19].**(Scheme.11)



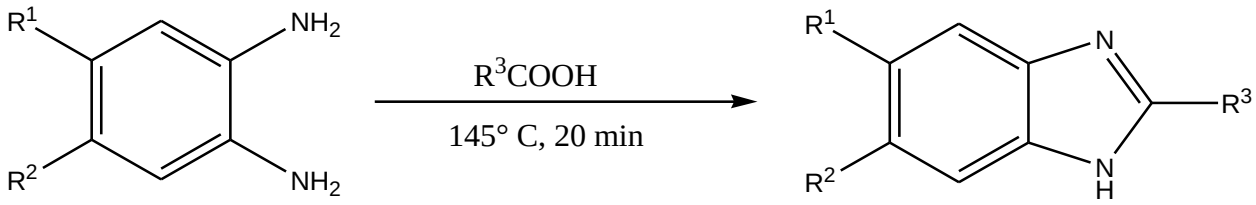
Scheme.11 Synthesis of Benzimidazoles from D-Glucose with o-Phenylenediamines in Water

11) One of the methods for synthesis is in the presence of PPA (5 mL), a mixture of o-phenylenediamine and organic acid in 10mmol and 15 mmol concentration respectively. This mixture is stirred and kept in a household microwave oven for 6 to 8 minutes at 162 W. After completion of reaction, we will let the solution to cool down and then pour it in the cold water. After stirring the mixture for several minutes and mixture is neutralized with aq. NaOH and then solid product is filtered out. Then crude product is purified by recrystallization**[20].**(Scheme.12)



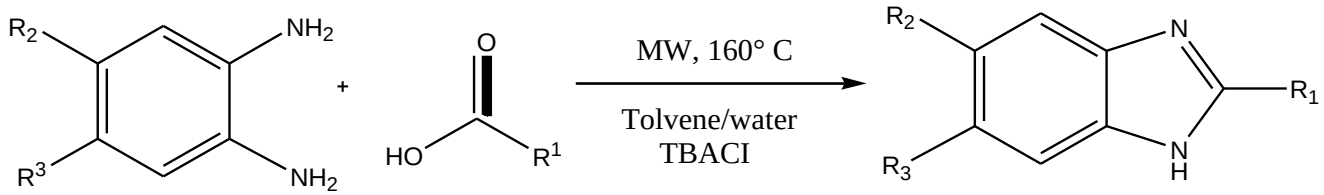
Scheme.12 Synthesis of 2-substituted benzimidazoles from o-phenylenediamine and PPA

12) When eight phenylene diamines and three carboxylic acids are reacted at 145 °C for 20 min, the desired 24 benzimidazoles are obtained, to a high yield of 40% to 95% with excellent purity**[21].** (Scheme-13)



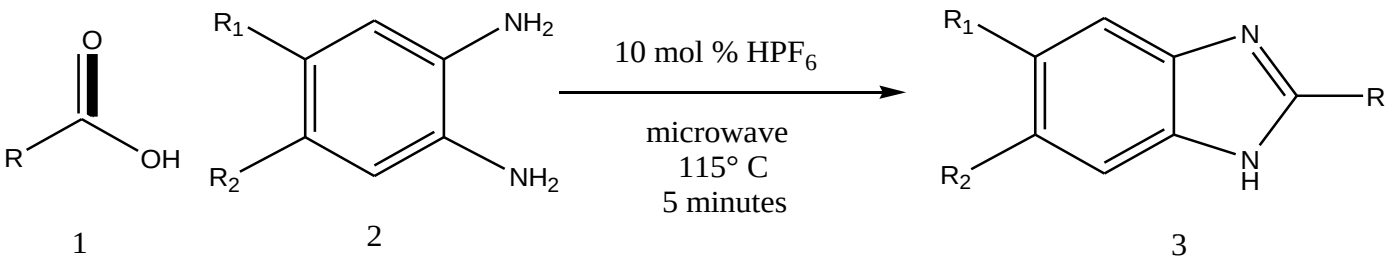
Scheme.13

13) If we take 1,2-phenylenediamine (1eq), carboxylic acid (1eq) and TBACI (0.1 eq) in microwave Pyrex tube. 10mL iodine and 10mL of water is added and get heated in microwave at 160 °C for mandatory time. When the reaction is completed, the mixture cools down at room temperature and alkaline is formed after the formation of the ammonia solution. The mixture is extracted with ethyl acetate and separated organic layer is dried over Na_2SO_4**[22].**(Scheme.14)



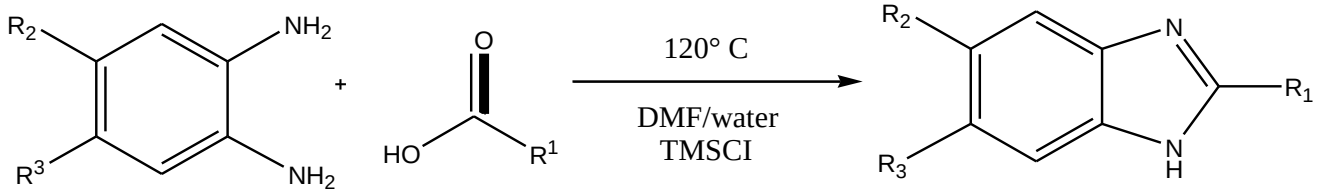
Scheme.14

14)A simple method of synthesis of 2-alkyl substituted benzimidazoles is by reacting aliphatic acid with the ortho-phenylenediamines in presence of hexafluoro phosphoric acid as catalyst under microwave heating at 115 °C for minutes**[23].** (Scheme.15)



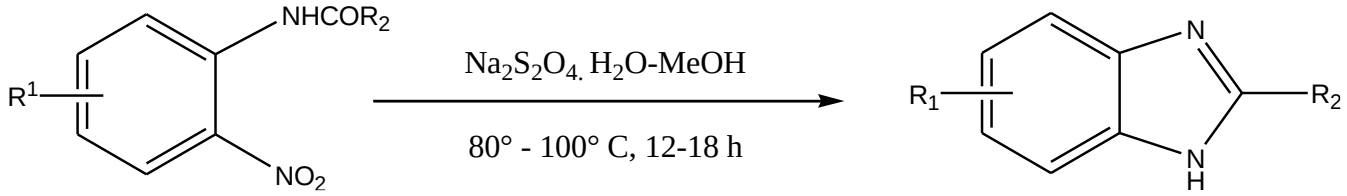
Scheme.15 Synthesis of 2-alkyl substituted benzimidazoles from aliphatic acid and ortho-phenylenediamines in presence of HPF_6

15) One of the easiest methods of synthesis of substituted benzimidazoles can be done by using TMSCI in proper catalytic amount which lead to high percentage of conversion**[24].** (Scheme.16)



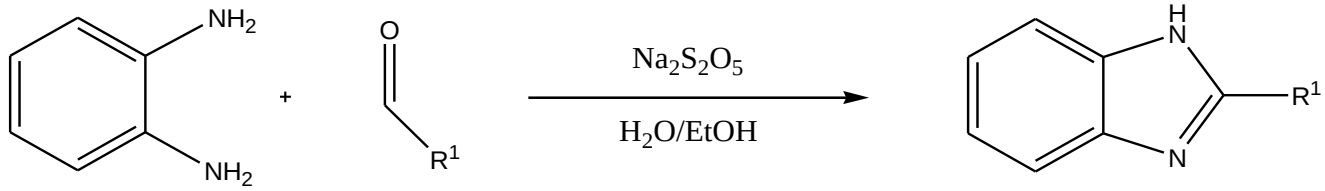
Scheme.16

16)A o-nitro anilide (1.0mmol) aqueous solution is treated with solid $Na_2S_2O_4$ (3.5 mmol) at 80°C and reaction mixture is get heated at 100°C for 18 hours and after completion of reaction it is cooled at room temperature. On removing of co-solvent, residue is treated with drop-drop addition of 5N aq. NH_4OH (2mL). The filtered precipitate formed is then washed with water and dried at reduced pressure and desired product is obtained**[10].** (Scheme.17)



Scheme.17

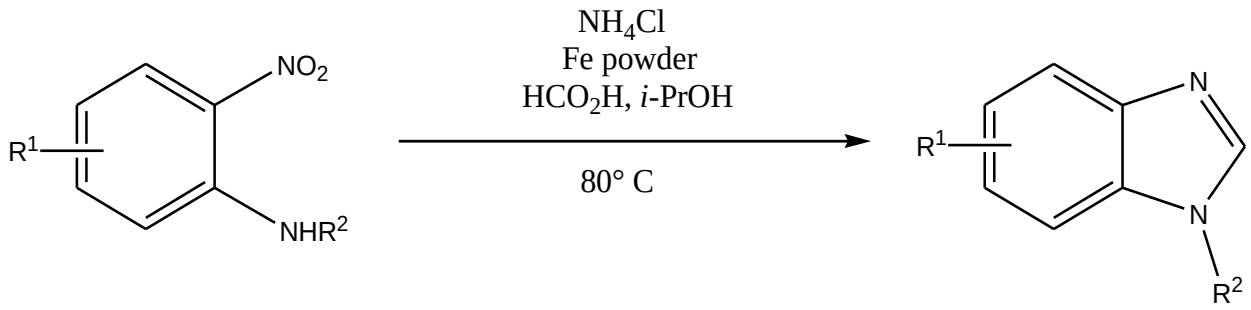
17) In stirring solution of o-phenylenediamine derivative (5 mmol) freshly prepared aqueous $Na_2S_2O_5$ is added and corresponding aldehyde (5.5 mmol) in ethanol. The mixture is submitted to react in for required time at 74 ±2 °C using a normal heating mantle. Then the crude of the reaction is cooled down and poured on stirred cold water. After drying of precipitate, it is purified by preparative chromatography by using hexane/ethyl acetate. Spot is extracted with acetone and dried to obtain pure compound i.e., benzimidazoles**[25]**.(Scheme.18)



Scheme.18

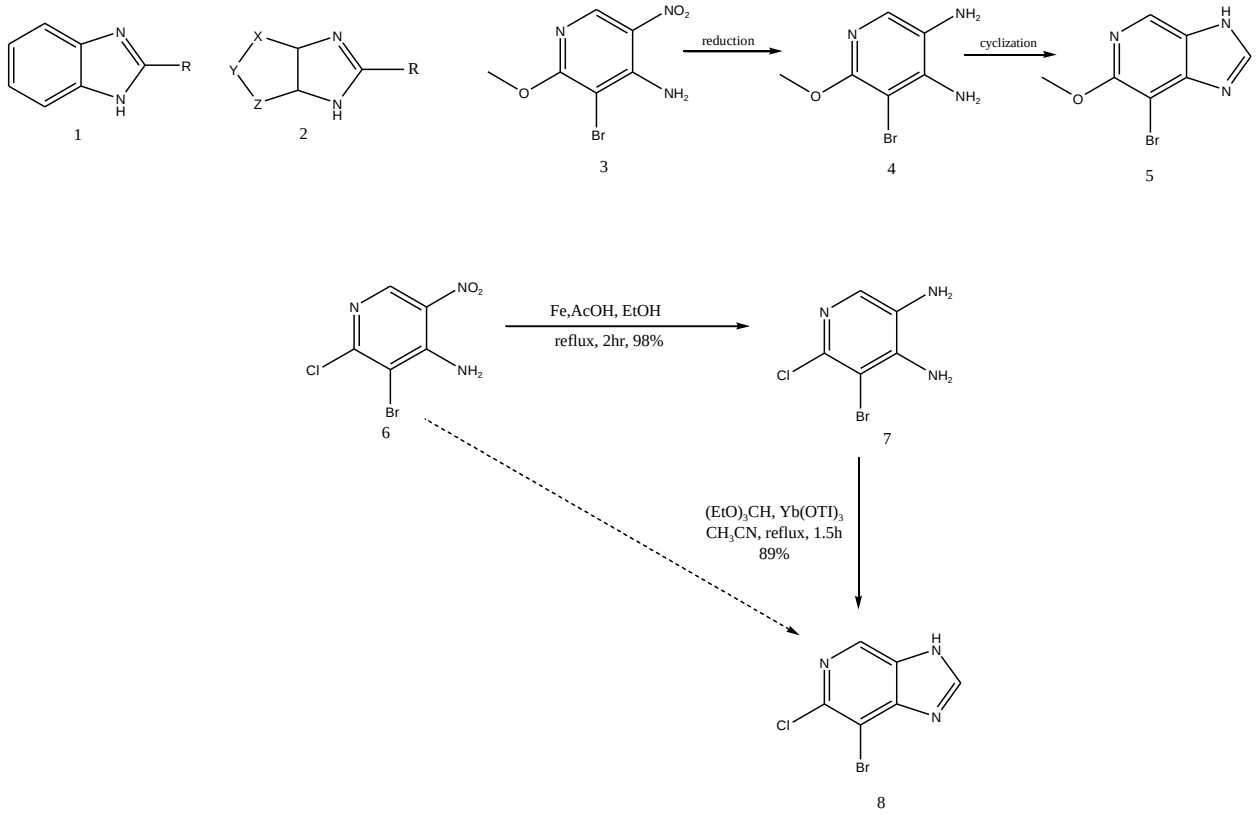
18) NH_4Cl has broader functional-group compatibility, and suitable for aqueous HCl. After procedure molar ratios of both iron powder and NH_4Cl, the presence and type of co-solvent, time, and temperature of the reaction, were established for optimal conditions**[26]**.

At these conditions, most reactions completed within one to two hours at 80 °C. A 10-equivalent excess of both iron powder and NH_4Cl provided optimal reaction times, 2–5 equivalents of each are sufficient to complete the transformation although reaction times extend to 24 hours. Similarly, a lower reaction temperature (60 °C) is sufficient but extends the reactions by several methods**[26]**. (Scheme.19)



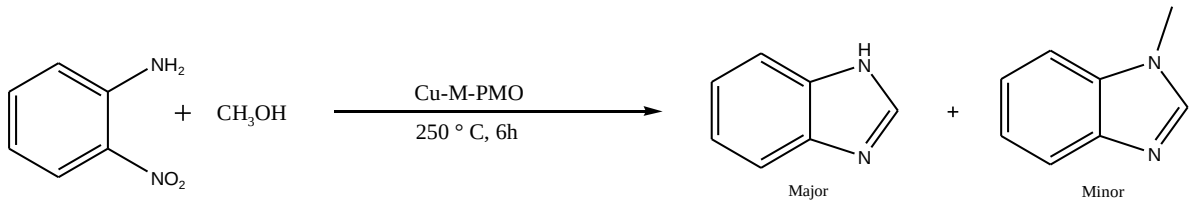
Scheme.19

19) This is a traditional method, which is carried out in a two-step process, firstly carrying the reduction of the nitro group followed by various condensation with the appropriate acid or Ortho ester. There have also been reports of a two-step synthesis in which the reduction and cyclization are carried out without isolating the corresponding intermediate ortho-diamine. This approach has been thoroughly explored, particularly in the synthesis of benzimidazole analogues**[27].**(Scheme.20)



Scheme.20

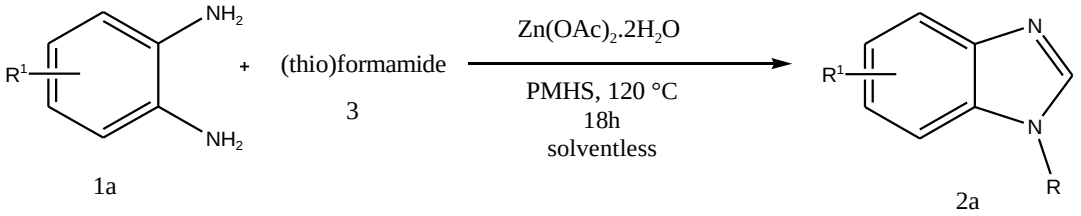
20) The variation of all porous metal oxides performed is shown in the following synthesis. This synthesis involves 1 mmol 1,2- diaminobenzene and 50 mg Cu-PMO catalyst at 280 °C for 2 hours afforded full substrate conversion. The two main reaction products were identified as benzimidazole 1a and N-methyl benzimidazole 1b, almost in equimolar ratio for each**[28].**(Scheme.21)



Scheme.21

21) At 120 °C, a 93% yield of the desired product 2a is produced within 18 hours. The yield of the desired product decreases as the reaction temperature decreases. Finally, we focused on the effect of PMHS loading on the reaction yield, highlighting the necessity of PMHS for the reaction.

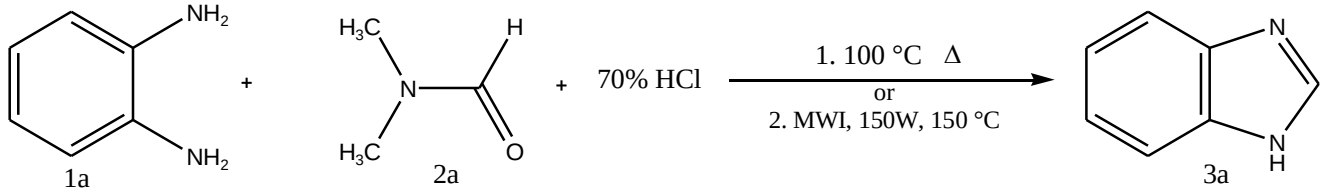
Furthermore, when we increased the amount of PMHS from 10 to 25 mmol, there was a decrease in the yield of the desired product 2a, accompanied by an increase in the yield of the methylated byproduct 2a′. Hence, the optimized reaction conditions were established as benzene-1,2-diamine (1a) (2 mmol), zinc (II) acetate di-hydrate catalyst, DMF (3; 10 mmol), and PMHS (5 mmol) at 120 °C for 18 hours**[29].**(Scheme.22)



Scheme.22

22) We can even obtain benzimidazole (3a) in 2 min when the mixture of 1,2-phenylenediamine (1a) in 70% HCl is irradiated by 150 W microwave radiations at 150°C with 96% yield.

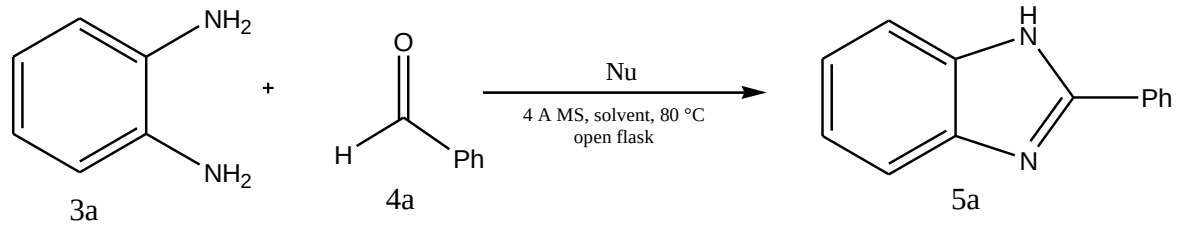
Reaction is carried out between 1,2-phenylenediamine (1a) but the reactions ended up with moderately good yields (40-78%) and time required for the completion of reactions was in the range from 1-12 hours. However, it was surprising to observe that the reactions progressed smoothly under microwave irradiation (150 W) at 150°C for 40-60 min with 80-95% yields**[31].**(Scheme.23)



Scheme.23

23) Nucleophiles are investigated as catalysts for the synthesis of benzimidazoles under the similar reaction conditions used for the benzoxazole synthesis.

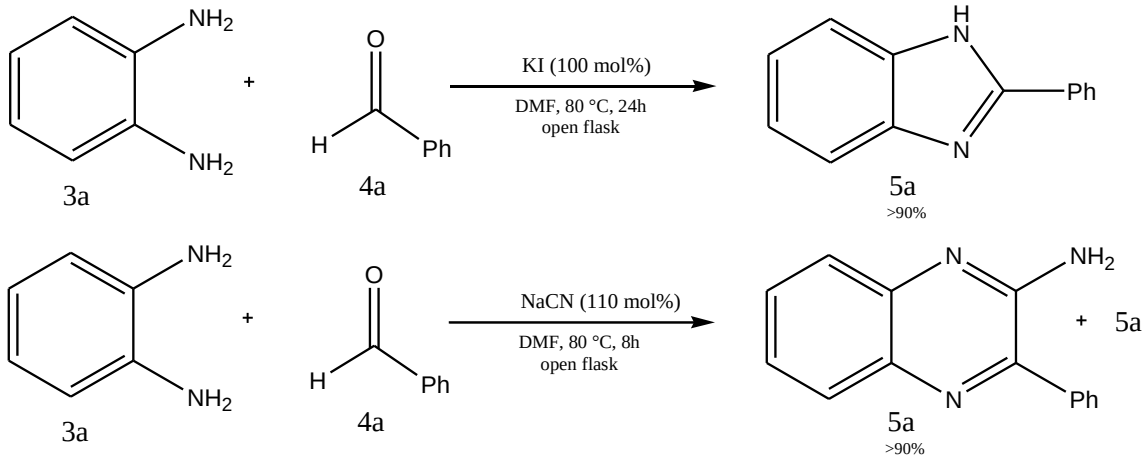
Iodide is found to significantly accelerate this transformation; benzimidazole 5a was obtained from ortho-phenylenediamine 3a and benzaldehyde 4a in an excellent yield in the presence of a stoichiometric amount of iodide at 80°C**[32].**(Scheme.24)



Scheme.24

24) When KI was used as a nucleophilic catalyst, the corresponding benzimidazole 5a was obtained in an excellent yield.

However, the reaction with Nan furnished 2- amino quinxoline 2 in low yield; benzimidazole 5a was obtained as the major product. **[32]**(Scheme.25)



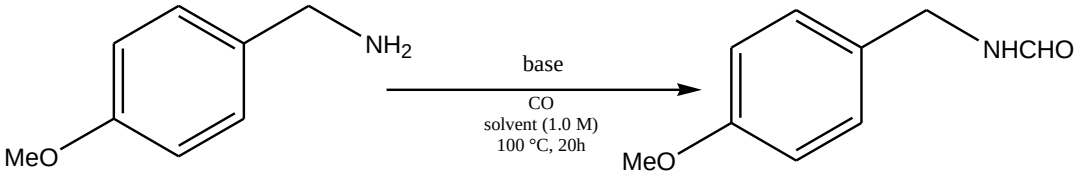
Scheme.25

The formation of benzimidazole 5a has never been achieved during our previous attempts in the synthesis ofbenzimidazoles with NaCN, we carefully compared the reaction conditions with those used previously for the synthesis of 2-aminoquinoxaline and found that molecular sieves were not accidently added to the reaction mixture. This result strongly suggested that water play a crucial role in this transformation**[32].**

25)TBD-CO adduct formation is optimized, which includes the pressure of CO, reaction temperature, and reaction time. TBD-CO adducts were formed with the best conversion when 30 bar of CO was applied at 100 °C for 18 hours.

First, forced CO with TBD is used, if TBD-CO adducts were formed in situ. TBD is used in toluene at 100 °C under 30 bars of CO to form product 1 with 33% yield. By increasing TBD to 1.5 equivalent, the

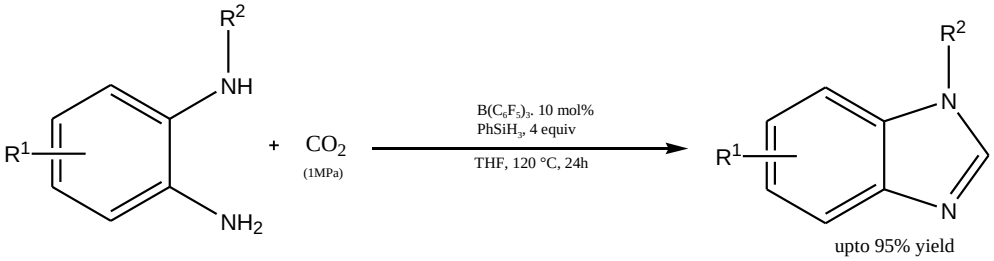
yield of 1 is increased to 90%. Following the reduction of CO pressure to 20 bars, the yield was decreased to 64%**[33].**(Scheme.26)



Scheme.26

26) The catalytic formation of benzimidazoles using CO_2 as a carbon source represents a shallow and maintainable approach to obtaining these valuable compounds. Herein, the B(C6F5)3-catalyzed synthesis of benzimidazoles via cyclization of o-phenylenediamines with CO_2 and $PhSiH_3$ is produced.

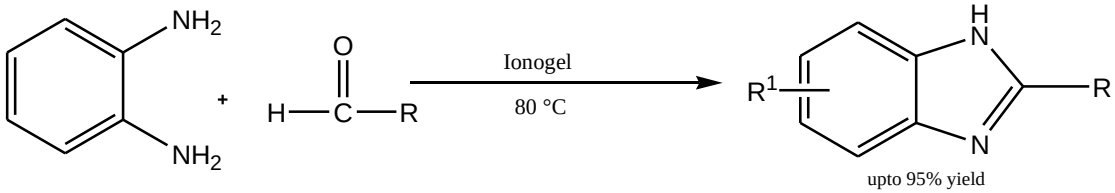
This metal-free catalytic route achieves the desired products in high yield under convenient reaction conditions and is applicable to a broad substrate scope. A plausible mechanism for the reaction involving a frustrated Lewis pair pathway is proposed based on spectroscopic characterization (e.g., 13C-NMR) of the reaction intermediates**[34].**(Scheme.27)



Scheme.27

27)A mixture of aldehyde (2 mmol), o-phenylenediamine (2 mmol) and ionogel (0.1 g) is taken in a round bottomed flask (100 mL) and stirred at 80°C on magnetic agitator under solvent-free circumstances.

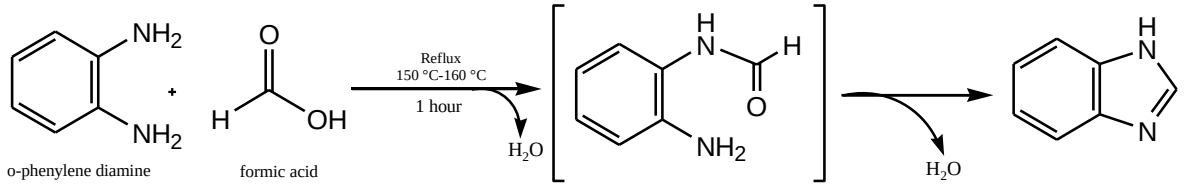
After completion of reaction (monitored by TLC), the reaction mixture is treated with ethyl acetate and filtered at pump under reduce pressure. The filtrate found is concentrated and kept at room-temperature until solid product is designed in crystalline form which is then slightly washed with pet ether and ethyl acetate in the ratio of 10:1 to obtain the invention in pure form**[35].**(Scheme.28)



Scheme.28

30) Here in this synthesis, benzimidazole is prepared by the mixture of O-phenylenediamine 1% and 90% formic acid through refluxed process at 150°C-160°C for 1h as shown in figure.

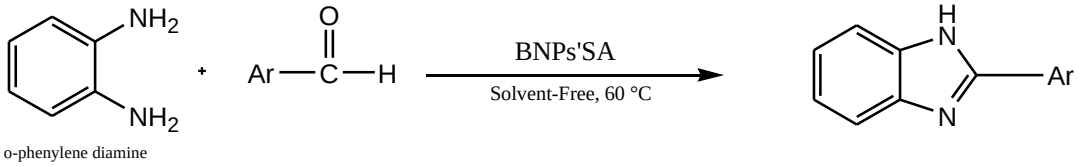
The invention found is filtered, splashed with water and dried at 100°C and selected as first multifarious, benzimidazole**[37].**(Scheme.31)



Scheme.31

31) Effects of different temperatures on rate of reaction to synthesis of 2-(4-chlorophenyl)-1H-benzo[d]imidazole is studied. At room temperature, the reaction takes long time and low yield, and the catalytic action is increased with evolution in temperature up to 100°C. Therefore, the reaction is kept at 60°C temperature.

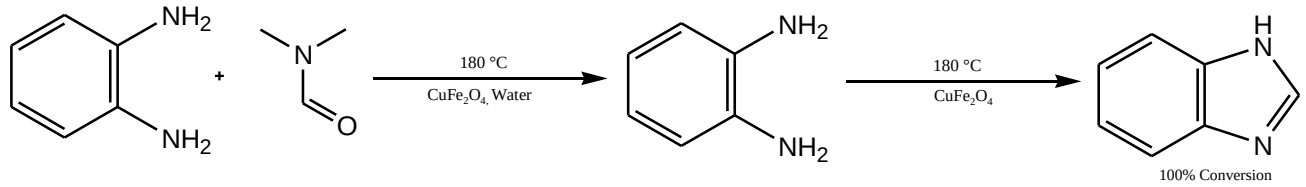
Solvent plays a vital role in the responses; therefore, in this research, for evaluating the effect of solvent and finding the ideal reaction temperature, the prototypical reaction is performed under different reaction conditions. The results collected show that 60°C and solvent-free conditions remained in the optimum reaction conditions for synthesis of benzimidazoles derivatives**[38].**(Scheme.32)



Scheme.32

32)A pure, simple and cost effective, synthesis of benzimidazole from o-nitroaniline using magnetically distinguishable $CuFe_2O_4$ catalyst. DMF in the existence of water rots to CO and dimethylamine. Later on, CO undergoes water gas shift reaction (WGSR) in the presence $CuFe_2O_4$ to form H_2 and CO_2. H_2 so generated reduces $-NO_2$ (o-nitroaniline) to $-NH2$ (OPD) in the presence of CuFe2O4 and further, OPD is cyclized to give benzimidazole through DMF as an essential carbon source. The formation of OPD as an intermediate is confirmed by GC–MS and NMR.

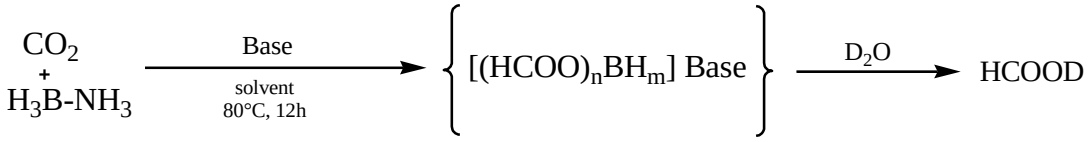
This type of synthesis has not been reported in the literature $CuFe_2O_4$ (nanospheres) were prepared by a well-known hydrothermal method consuming sodium acetate as a capping reagent. It forms an inverse spinal type of structure. Cu^{2+} occupies the octahedral site, whereas half of Fe^{3+} occupies tetrahedral sites. It can be expressed as (BIII) Tet (AIIBIII) $^{oct}O4$. It is widely used as a catalyst for WGSR. The fresh and reused $CuFe_2O_4$ catalysts remained considered by unlike analytical techniques**[39].**(Scheme.33)



Scheme.33

33) The reaction of CO_2 and BH_3NH_3 is then accomplished in the occurrence of triethylamine (Et3N) in CH_3CN at 80 °C.

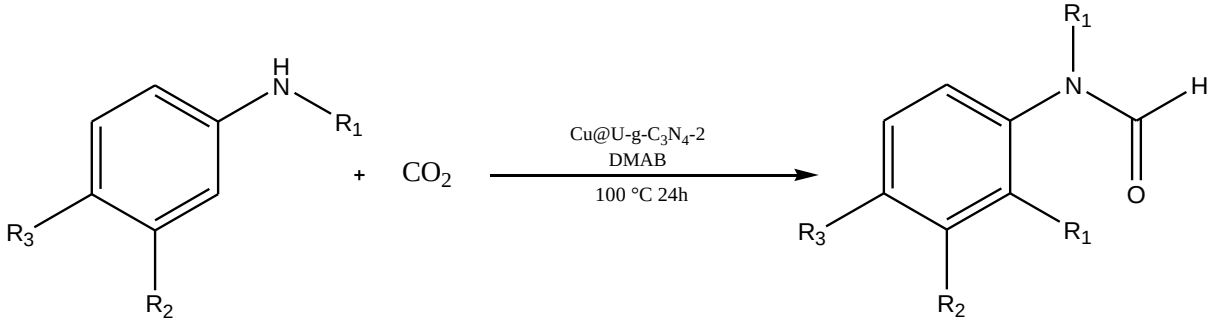
Now, the yield of HCOOD is determined by 1 H NMR integrations to be 87 % in D_2O based on the integration of the signal equivalent to the formyl group of HCOOD by using 1,1,2-trichloroethene as an interior standard and particular to BH_3NH_3**[40].**(Scheme.34)



Scheme.34

34) The formylation aniline and its derivatives were carried out using CO_2 and DMAB to obtain good yield of corresponding formanilide by the improved reaction. Furthermore, a cautious reaction mechanism for the synthesis of benzimidazole has been developed on previous methods.

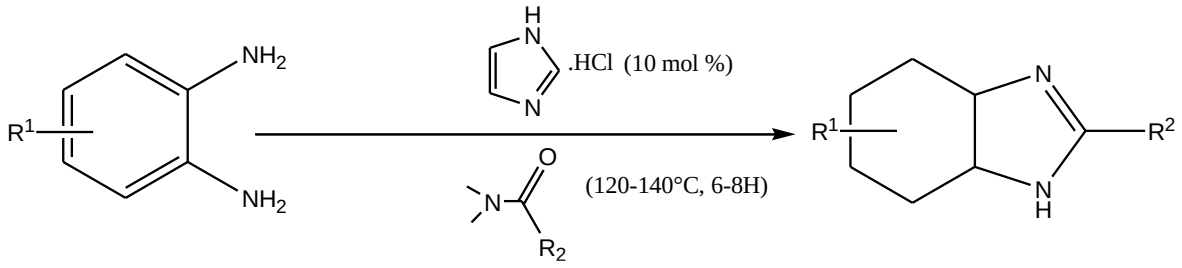
The Cu@U-g-C3N4 catalyst stimulates the DMAB to form intermediate 2 and catalysed by the addition of CO_2 into B–H bond for forming the intermediates**[41].**(Scheme.35)



Scheme.35

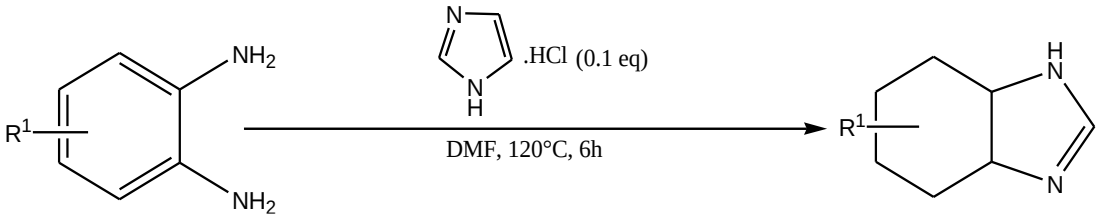
35) The synthesis of benzimidazoles and 2-substituted benzimidazoles is efficient and convenient synthesis which is fully desirable. The use of imidazolium chloride-based catalysis induced us to explore the use of imidazolium chloride as a catalyst in the formation of benzimidazoles.

Herein, the report of an efficient protocol for synthesis of benzimidazoles and 2-substituted benzimidazoles from o-phenylenediamines and DMF derivatives in the presence of imidazolium chloride without any other catalysts or additives under metal-free conditions is presented**[42].**(Scheme.36)



Scheme.36

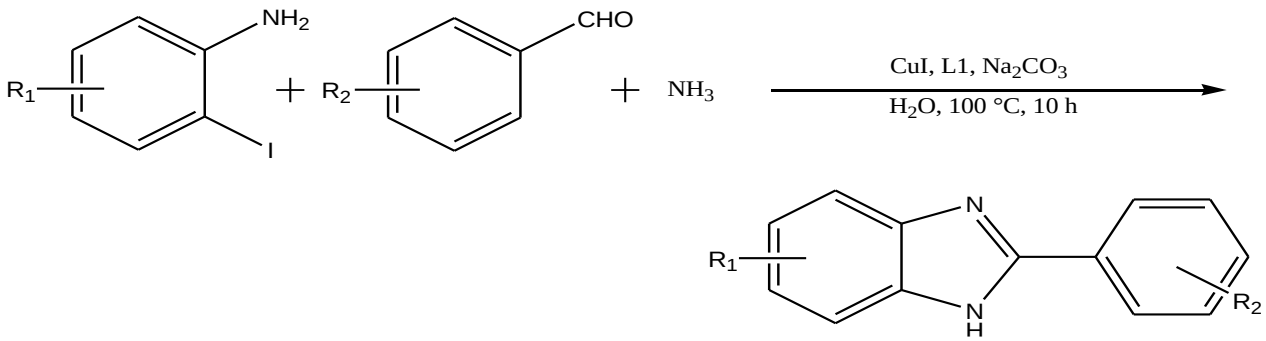
36) The synthetic usefulness of this reaction, we further illustrated its scalability.For delight, when the reaction was scaled up to 180 mmol (20 g scale), the desired product is isolated in 90% yield is Gram scale synthesis of benzimidazole**[42].**(Scheme.37)



Scheme.37

37) Ligands, L1 (1,10-phenanthroline) displayed the highest catalytic activity in 85% yield. Control experiments implied that the use of a metal and ligand is essential, only 10% or 17% of product were gained in the absence of a ligand or catalyst. Of the bases tested, Na_2CO_3 gave the best results.

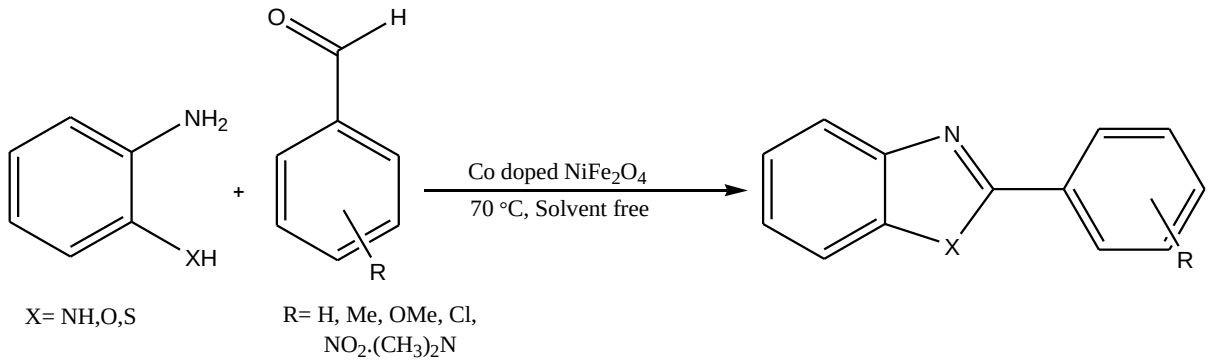
The product is formed in a lower yield with K_2CO_3, NaOH, K_3PO_4, KOH, and Cs_2CO_3. The effects of reaction time and temperature were also studied; 100 °C and 10 h were the optimal reaction conditions. Therefore, the optimal catalytic system involved the use of CuI (10 mol%), L1 (10 mol%), 25%–28% aqueous ammonia (1 mL) and Na_2CO_3 (2 equiv.) in 1 mL water at 100 °C for 10 hours**[43].**(Scheme.38)



Scheme.38

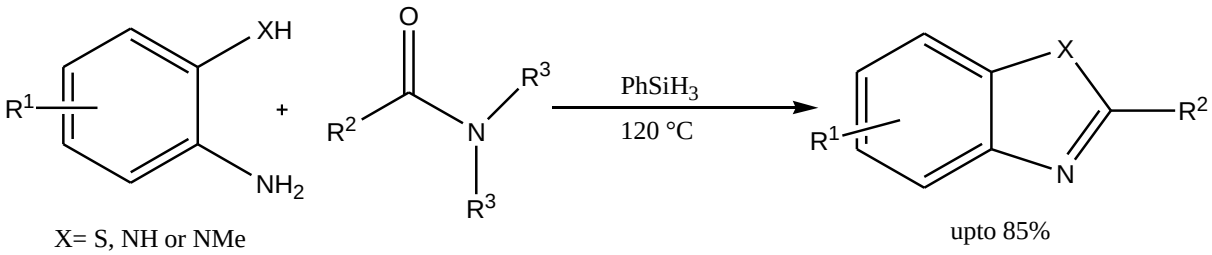
38) Study of the synthesis and use of Co-doped $NiFe_2O_4$ encouraged us to discover another aspect of the Co-doped $NiFe_2O_4$ as magnetic nano catalysts for the synthesis of benzimidazoles, from the reaction between o-phenylenediamine, o-aminophenol, o-amino thiophenol and a variation of substituted benzaldehydes under solvent-free conditions at 70°C.

This reaction was investigated using various amounts of the nano catalyst at 70°C. In the absence of the nano catalyst, the yield of the reaction was low. With the addition of the catalyst to the reaction mixture, the reaction happened with 60% yield. Further study showed that the best outcomes were obtained with 10 mol% catalyst, with 97% yield under similar conditions**[6].**(Scheme.39)



Scheme.39

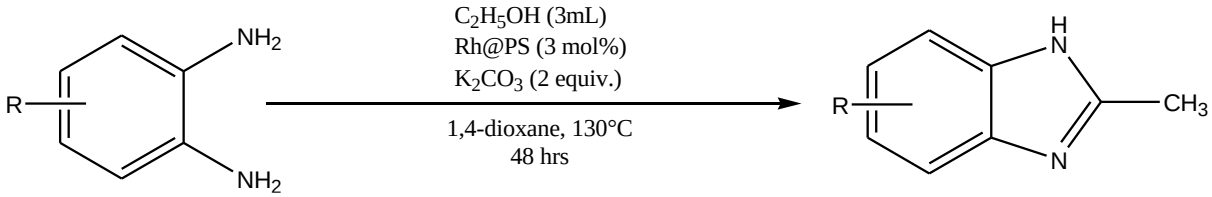
39) For our ongoing research the synthesis of valuable benzimidazole compounds, we auspiciously found a well-organized protocol for the synthesis of benzimidazoles from o-phenylenediamines and DMF derivatives retaining $PhSiH_3$ as the only organizer without any other catalysts or extracts under metal-free conditions**[44].**(Scheme.40)



Scheme.40

40) The various quantity of bases, solvents, catalyst loadings and temperature, found that 1,2-phenylenediamine (100 mg), ethanol (3 mL), Rh@PS (3 mol% Rh), K_2CO_3 (2 equiv.) and 1,4- dioxane (1.5 mL) as co-solvent at 130°C is the best reaction condition for the synthesis of 2- methyl benzimidazole.

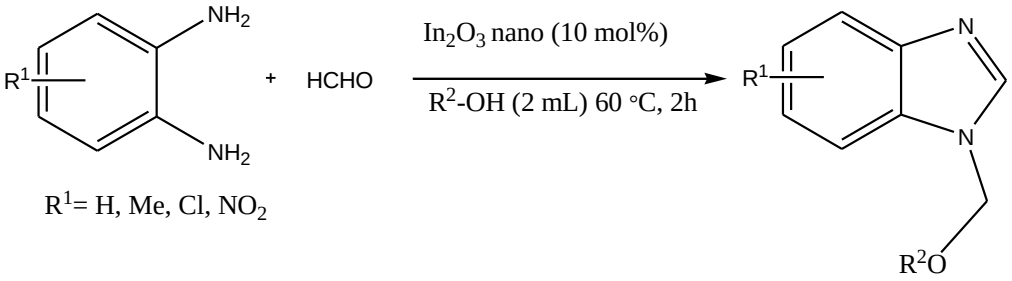
This procedure is further applied to the electron rich and deficient substituted 1,2-phenylenediamines. With an electron donating substituents as 3-methylbenzene-1,2-diamine, 4,5-dimethyl-1,2-phenylenediamine afforded the anticipated product in exceptional yields**[45].**(Scheme.41)



Scheme.41

41) The practice of indium oxide nano (In_2O_3) mediated in the area of organic synthesis is very significantly imperfect. As a continuation of our previous work on indium oxide nano, here we are delighted to report an appropriate synthesis of N-substituted benzimidazole derivatives (N-alkoxylate benzimidazoles) by the multicomponent reaction (MCR) of ortho-phenylenediamines (OPDs) with formaldehyde and alcohol in presence of indium oxide nano particle (In_2O_3) via intermolecular cyclization**[46].**

For our best knowledge, the first-time report for the synthesis of N-alkoxylate benzimidazoles derivatives synthesized in a one pot synthesis fashion. (Scheme.42)

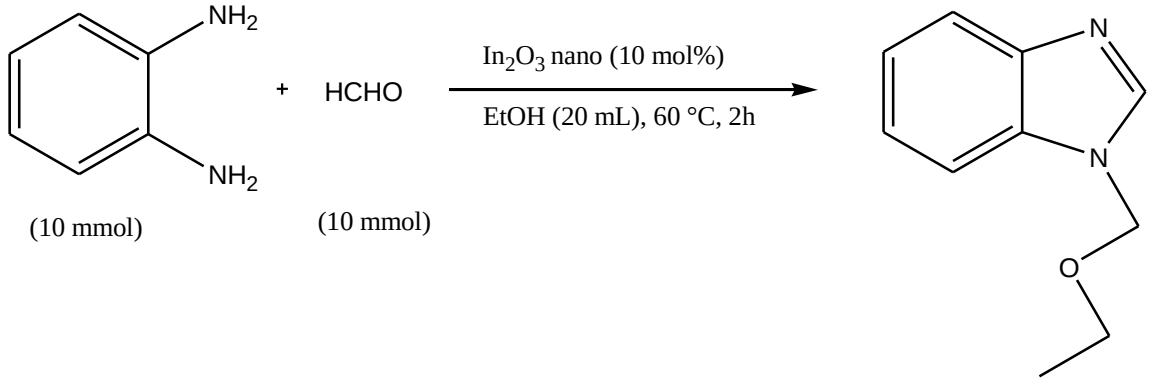


R^1= H, Me, Cl, NO_2

Scheme.42

42) The synthetic pertinency of this procedure is examined on the gram scale using the classical reaction in laboratory setup.

The response could afford 1.27 g in 72% yield without any important loss of its productivity, demonstrating the potential requests of the current method for a large-scale synthesis of N-alkoxylate benzimidazole derivatives.**[46]**Scheme.43)

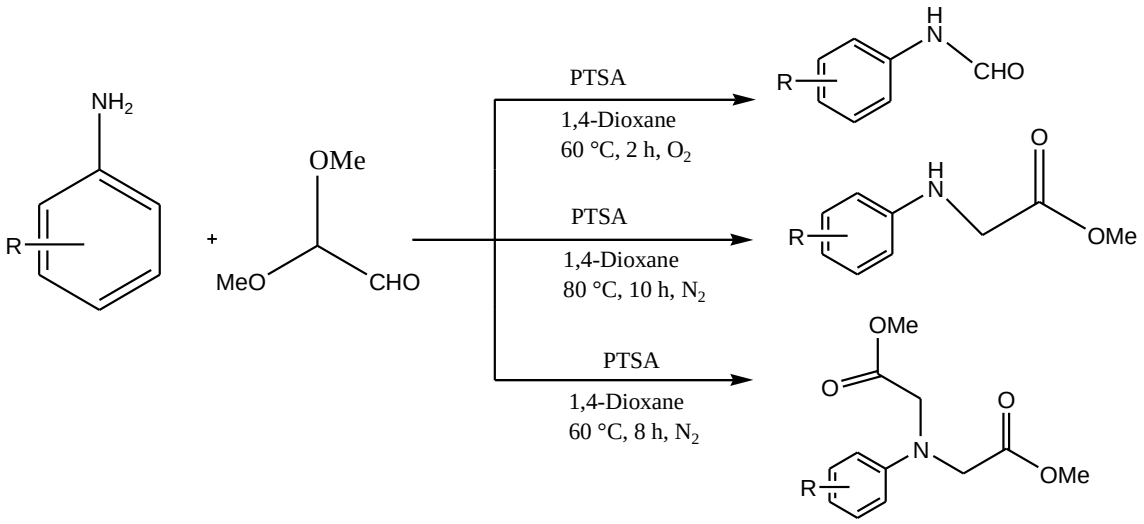


(10 mmol) (10 mmol)

Scheme.43

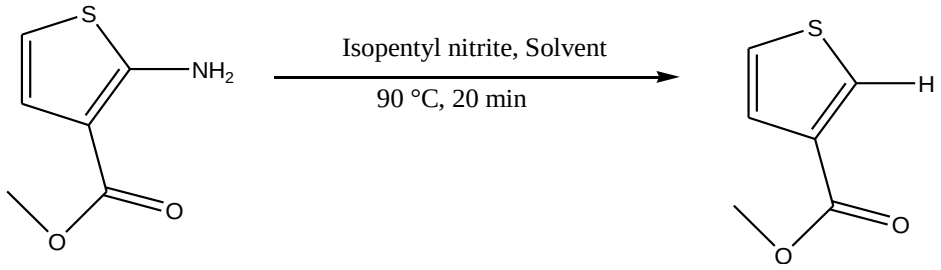
43) Acid-catalyzed chemo divergent reactions of 2,2-dimethoxyacetaldehyde and anilines stayed defined, which were realized via either a C−C bond cleavage or a Heyns rearrangement of the reaction intermediate.

These reactions not only enriched the conversion method of biomass-derived platform molecule, 2, 2-dimethoxy acetaldehyde, but also presented simplistic and efficient ways for the synthesis of methyl phenylglycinate**[47].** (Scheme.44)



Scheme.44

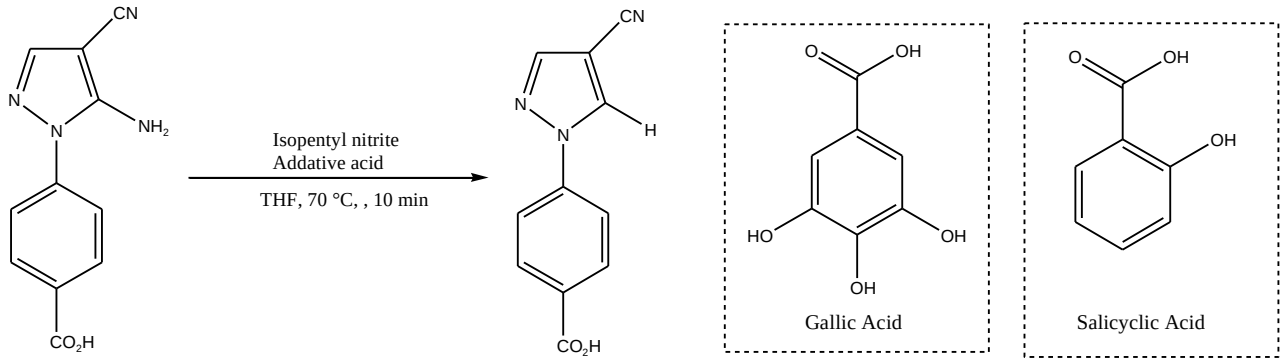
44) Methyl 2-aminothiophene-3-carboxylate (1.0 mmol) in the stated solvent (10 mL), iso-pentyl nitrite (1.2 mmol) in the stated solvent (10 mL), both flowing at 0.25 mL min−1 through a 10.0 mL coil reactor maintained at 90 ◦C (residence time: 20 min). The conversions were calculated by integration of product 1H-NMR peaks relative to a quantified internal standard of nitrobenzene. THF—tetrahydrofuran**[48]**.(Scheme.45)



Scheme.45

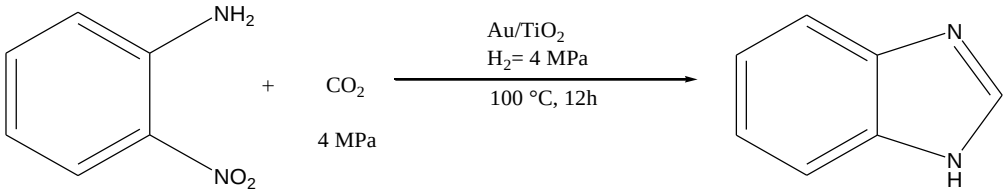
45)4-(5-amino-4-cyano-1H-pyrazol-1-yl)-benzoic acid (1.0 mmol) and the stated amount of gallic acid or salicylic acid in THF and iso-pentyl nitrite (1.2 mmol) in THF (50 mL), flow rate 1.0 mL min−1, through a 10 mL coil reactor preserved at 70 °C, for a time of 10 min.

The conversions were planned by combination of product 1H-NMR peaks relative to a quantified internal standard of nitrobenzene. Reaction accomplished at 120°C**[48].**(Scheme.46)



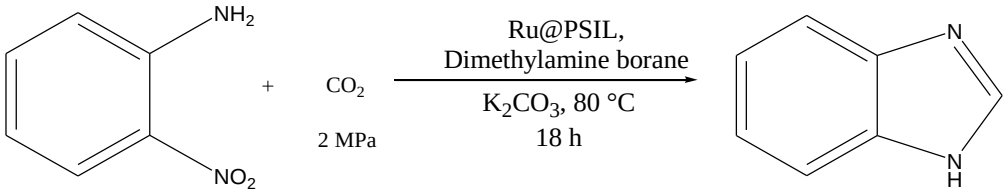
Scheme.46

46) The direct conversion of o-nitroaniline to benzimidazole in the presence of CO_2 atmosphere. Hao et al. reported Au/TiO_2 catalyst for the synthesis of benzimidazoles from o-nitroaniline and H_2 as a reducing agent in the presence of CO_2 (CO_2 and H_2 = 8 MPa) at 100°C for 12 hours**[17].**(Scheme.47)



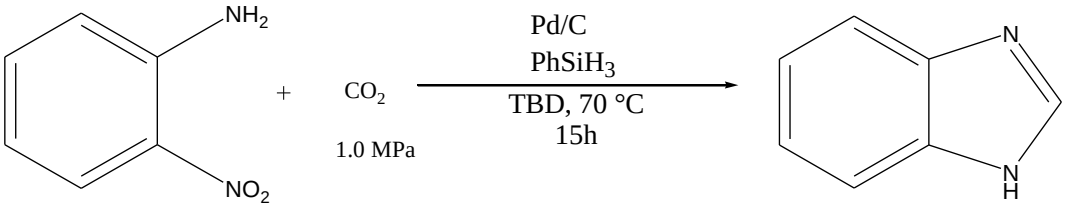
Scheme.47

47) The synthesis of formamides and benzimidazoles from amines, nitrobenzene and o-nitroaniline catalyzed by Ru@PSIL has been reported. N-formylation of amines is obtained by using Pd-NC-800 catalyst in presence of 7 MPa pressure (H_2: CO_2 – 4:3) at 80°C**[17].**(Scheme.48)



Scheme.48

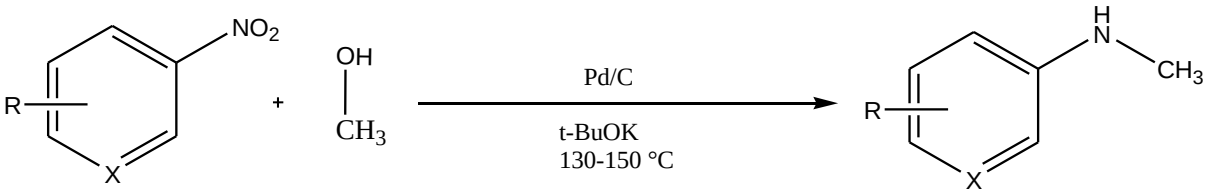
48)A more efficient, simple and sustainable route for the synthesis of benzimidazoles from o-nitroaniline is the efficient synthesis of benzimidazole directly from ortho nitroaniline, phenyl silane as a reductant, ACN (acetonitrile) as a solvent in the presence of CO_2 atmosphere at 70°C for 15 hours**[17].**(Scheme.49)



Scheme.49

49) Carbon-supported-palladium (Pd/C)-catalyzed N-methylation of nitroarenes and amines by means of MeOH as both a C1 and a H_2 source. This transformation proceeds with high atom-economy and in an ecologically welcoming way via copying hydrogen mechanism.

A total of >30 structurally diverse N-methylamines, including bioactive compounds, were selectively synthesized with isolated yields of up to 95%. Furthermore, selective N-methylation and deuteration of nimesulide, a nonsteroidal anti-inflammatory drug, were understood through the late-stage functionalization**[49].**(Scheme.50)

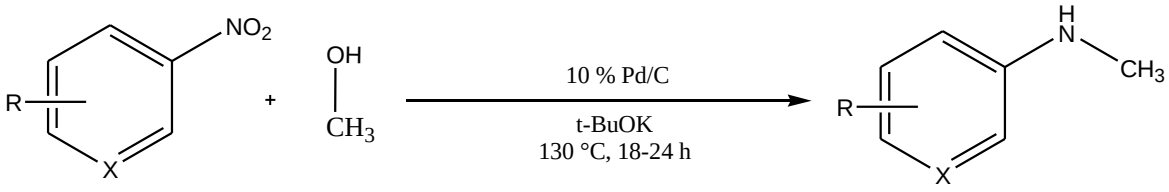


X= C, N

Scheme.50

50) Suitable reaction conditions for selective mono-N-methylation of nitrobenzene, were explored as the scope and limitations with a wide range of nitroaromatics using MeOH as a C1 and H_2 source.

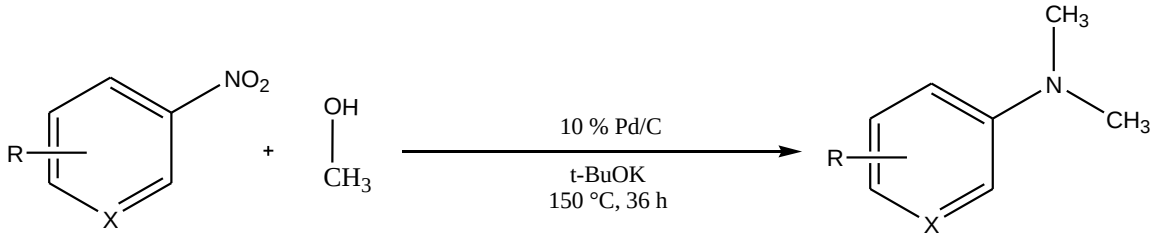
Accordingly, 4.7 mol % 10% Pd/C, 4 equivalent of t-BuOK, and 2 mL of methanol at 130 °C and 20 hours were considered as optimal reaction conditions for selective mono-N-methylation of nitroarenes**[49].**(Scheme.51)



X= C, N

Scheme.51

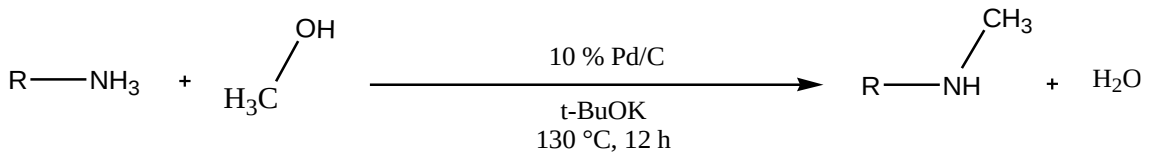
51)0.5 mmol of nitroarene, 10% Pd/C (4.7 mol % Pd, 25 mg), 2 mL of MeOH as a reagent and solvent, t-BuOK (2 mmol, 4 equivalent), 36 h, 150 °C, isolated yields**[49]**.(Scheme.52)



X= C, N

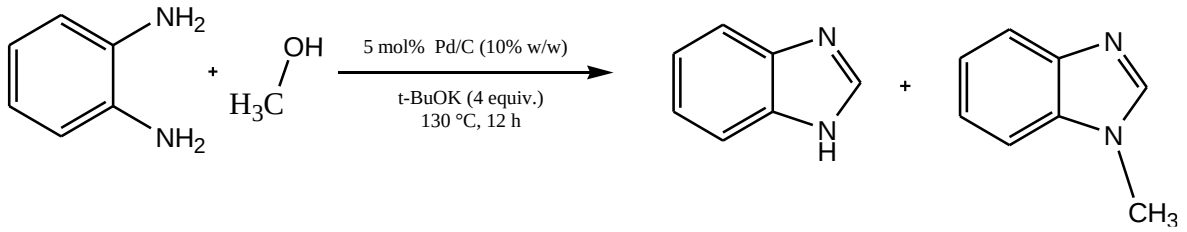
Scheme.52

52)0.5 mmol of amine, 10% Pd/C (4.7 mol % Pd, 25 mg), 2 mL of MeOH as a reagent and solvent, t-BuOK (1 mmol, 2 equivalent), 12 h, 130 °C, isolated yields**[49].**(Scheme.53)



Scheme.53

53) Ortho-phenylenediamine (0.5 mmol), 10% Pd/ C (4.7 mol % Pd, 25 mg), 2 mL of MeOH as a reagent and solvent, t-BuOK (2 mmol, 4 equivalent), 130 °C, 12 hours**[49].**(Scheme.54)



Scheme.54

Conclusion-

The biological activity of a drug depends largely on its physicochemical properties, which can be improved by structural diversity. The benzimidazole scaffold has been largely used in making clinical candidates owing to its substituents bearing capacity at multiple centers, which has not only been useful in sharpening the potency but also helps in improving pharmacokinetics. From an overall pursual of the literature, it is observed that numerous benzimidazole analogues were useful against several microbes, but the fatal side effects and drug resistance are the two biggest challenges to the researchers. The overwhelming clinical responses of benzimidazole derivatives often encourage putting endeavors towards better research. In this review several forms of benzimidazoles were soon along with their biological properties and synthetic strategies were also described which gives more yield than other conventional methods.

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