MULTI COMPONENT GREEN APPROACH FOR SYNTHESIS OF 1, 2-DISUBSTITUTED BENZIMIDAZOLE

Abstract

The process described here to synthesis 1,2-disubstituted benzimidazole is very easy, inexpensive and eco-friendly. The method involves the sequence of processes coupling-reduction-cyclization in one-pot under eco-friendly conditions.

Keywords: Benzimidazoles, Solvent free, Cyclization, One-pot synthesis, Greener Approach, Substitution.

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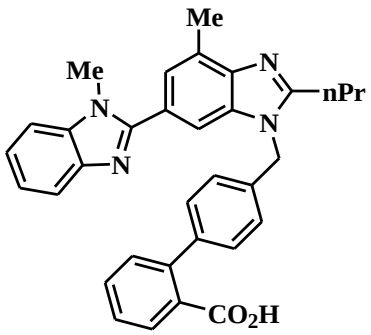
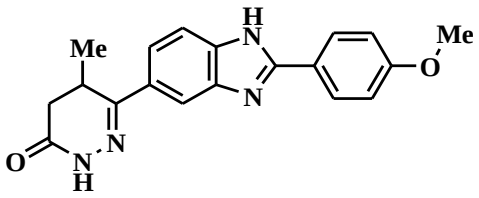
I. INTRODUCTION

Nitrogenousheterocycles are found everywhere in nature and they are necessary for living system.Their role in the metabolism of living cells is ubiquitous. Also, benzimidazole derivatives are widely used as heterocyclic skeleton in pharmaceutical chemistrydue to its ability to demonstrate a wide range of biological activities. (Figure1)[1]. Compounds with benzimidazole scaffoldsare used as antiulcer, anti-inflammatory, antibacterial, anticarcinogens and peptic ulcer agents.A variety of bioactive chemicals, including nonpeptide luteinizing hormone-releasing hormone (LHRH) antagonist, nonpeptide thrombin inhibitor, and 5-lipoxygenase inhibitor, contain benzimidazole and its derivatives as a key structural motif. Additionally, they have gained a lot of attention because to their many applications[2] as chemo sensors, polymers, dyes that operate as enzyme inhibitors, and fluorescence probes. The manufacture of medicines and fine chemicals, on the other hand, is relying more and more on amino acids. They play a significant role in organic synthesis as chiral synthons and directing auxiliaries. They are widely utilized as essential ingredients in insecticides, anticoagulants, reproductive medicines, and lactam antibiotics.



Micardis
antihypertension drug (1)



Pimobendan
Calcium sensitizer drug (2)

Figure 1: Drugs with Benzimidazole as Basic Skeleton

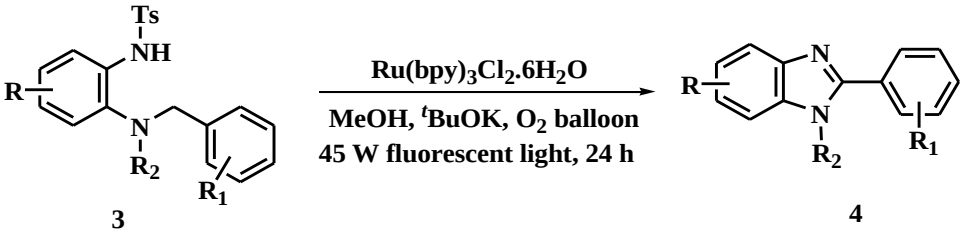
Many therapeutic medications, including proton pump inhibitors Protonix, Prilosec, Atacand (hypertension), and broad spectrum anthelmintic Verm ox, as well as other investigational drug compounds, include benzimidazole derivatives. As a result, the efficient synthesis of benzimidazole scaffolds has always been an interesting topic in organic synthesis. Benzimidazoles are generally prepared from *ortho*-aryl diamines, which can be obtained by ortho nitrification of aniline followed by reduction of the nitro moiety. The two main synthetic strategies for the production of benzimidazoles are: (i) condensation of *ortho*-aryl diamines with carboxylic acids and their derivatives and (ii) condensation of *ortho*-aryl diamines with aldehydes to produce benzimidazoles Intermediate dehydrogenation. Both methods have serious problems.The former must be very acidic and sometimes have high temperatures, while the latter must have stoichiometric or excessive oxidants. Effective use of benzimidazoles from 2-haloacetanilides, N-arylbenzamidines, 2-haloarylamidines, transition metal-catalyzed aryl amination, C-H functionalization and oxidation of alcohols has been recently reported. However, each link requires some intervention to prepare the first product.

II. SYNTHESIS OF BENZIMIDAZOLE[3]

Although many methods have been reported for the synthesis of 1- or 2-monosubstituted benzimidazoles, the synthesis of 1,2-disubstituted benzimidazoles still faces problems of controlling regioselectivity, increasing efficiency, and making it more general. Most methods, such as the condensation of carboxylic acids with N-substituted 1, 2-diaminoarenes and N-arylation/alkylation of 1H-benzimidazoles, are for 1, 2-disubstituted benzimidazoles because there is a problem and are often limited in scope. Mix of the two. regional isomers the difference between two N atoms.

Alternatively, palladium, copper, indium, ruthenium, and cobalt-catalyzed intramolecular N-arylations from o-haloaniline/ o-halonitrobenzenes were used. However, most of these methods involve multiple synthetic process modifications and involve complex separation processes, resulting in high costs and/or lack of starting materials. In some cases, the use of strong acid catalysts also limits the performance of the tolerance group.

1. **Using Iminium Ion and A-Aminoalkyl[4]:** In 2016, Z. Zhang et al. reported a competitive intramolecular cyclization/deprotection sequence by combining two different photocatalytic cycles (including iminium ion and α-aminoalkyl radical pathways) under visible light photoredox conditions to produce multisubstituted benzimidazole derivatives.(Scheme1).



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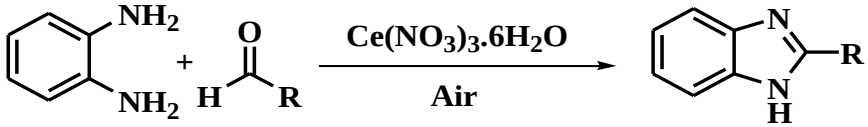
Scheme 1: Visible-Light Induced Synthesis of Multi-Substituted Benzimidazoles

2. **Using Ce $(No_3)_3.6h_2o$[5]:** In 2017, S. R. Mendes *et al.*reported the synthesis of 2-Substituted benzimidazoles (Scheme 2). This process avoids the use of toxic metal catalysts as well as additional bases and oxidants. They simply heated 1,2-diaminobenzene and aldehydes in DMF at 80 ^{o}C, in presence of $Ce(NO_3)_3.6H_2O$ as promoter and atmospheric oxygen as an efficient oxidant.



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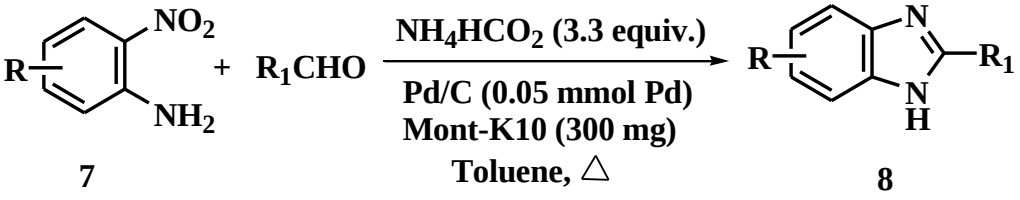
Scheme 2: Ce $(NO_3)_3.6H_2O$ Promoted Synthesis of 2-Substituted Benzimidazoles

3. **Using Combined Pd/C and Montmorillonite Catalysis[6]:** In 2012, J. Magolan *et al.*have synthesized benzimidazoles through one-pot hydrogenation, condensation and dehydrogenation using montmorillonite-K10 and Pd/C catalysts simultaneously as two

types of heterogeneous catalysts (Scheme 3). This strategy was also adopted to complete the five-step, three-component synthesis of antibacterial benzimidazoloquinazolines using a simple one pot method.



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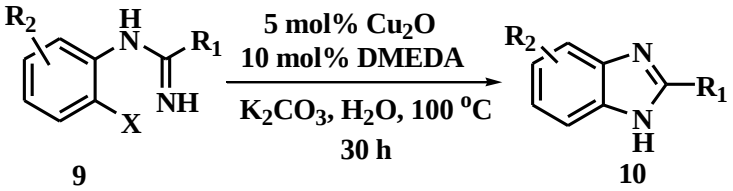
Scheme 3: One Pot Synthesis of Benzimidazoles Catalyzed by Pd/C and Montmorillonite.

4. **Using Copper-Catalyzed**[7]: In 2011, C. Chen and co-workersdiscovered a simpler, more efficient and more efficient method for copper-catalyzed intramolecular N-arylation, providing a key element, the benzimidazole ring (Scheme 4). This process uses Cu_2O together with a simple diamine derivative (DMEDA) as a catalyst under mild conditions. Additionally, the use of water as a solvent would make the process described here economical, environmentally friendly, and useful for commercial use.



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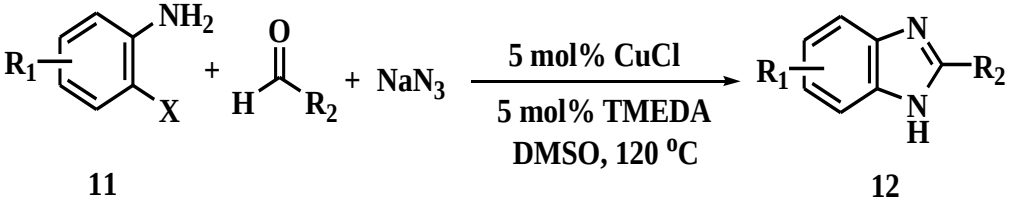
Scheme 4: Benzimidazole Derivatives using Copper Catalyst

5. **Using Copper Catalysed Synthesis Through C-N Bond Formation**[8]: In 2011, S. Lee and co-workers have developed the synthesis of benzimidazoles by the reaction of 2-haloaniline, aldehyde and NaN3 in the presence of 5% mol of CuCl and 5% mol of TMEDA in DMSO was carried out at 120°C for 12 hours (Scheme 5).



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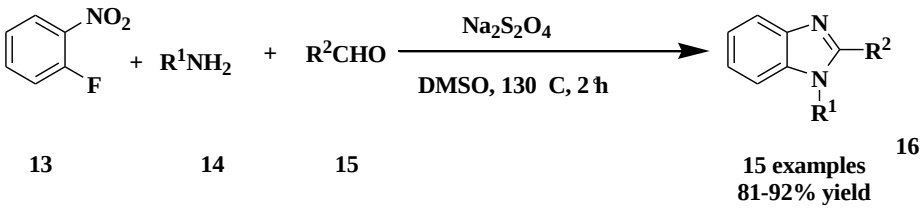
Scheme 5: Synthesis Benzimidazole Derivatives through C-N Bond Formation Using Copper as Catalyst

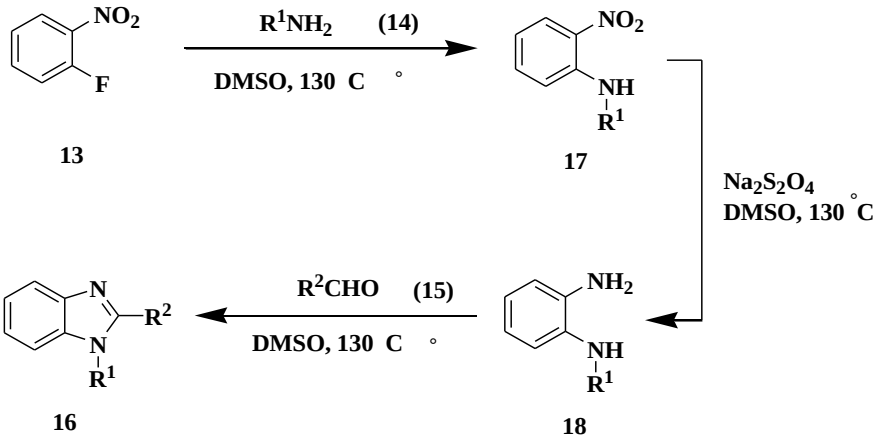
III. MULTICOMPONENT COUPLING REACTION (MCR) APPROACH TOWARDS BENZIMIDAZOLE SYNTHESIS[9]

In 2011, we have developedone-pot method to access benzimidazole rings in neutral metal-free conditions. This multi-component reaction sequence gives good yields in all cases (Scheme 6).



Scheme 6: Synthesis of Benzimidazoles under Metal Free Condition

Stepwise the reaction sequence are(i) activated nucleophilic substitution of 1-fluoro-2-nitrobenzene **13**with a primary amine **14**, (ii)sodium dithionite induced reduction of coupled nitroarene **17**, and (iii) coupling of an aldehyde **15**with the corresponding diamine **18**(Scheme 7).



Scheme 7: Strategy towards Dynthesis of Benzimidazoles

What is Multicomponent Coupling Reaction (MCR)?

MCR is a method of mixing three or more compounds in a reaction vessel to produce a product containing substantial portions of all starting materials.

1. Advantages of MCRs

- **Intrinsic Aspect**
  - Superior atom economy
  - Atom utilization
  - Selectivity
  - Reduces by-products
- **Extrinsic Aspects**
  - Simpler procedure and equipment's
  - Reduction of cost, time and energy

We had done the pentannulation reaction in different reaction conditions. It has been shown that temperature of the reaction and solvent have a significant effect on

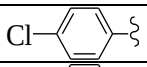
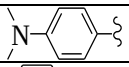
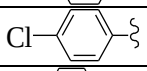
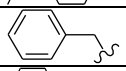
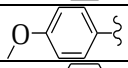
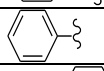
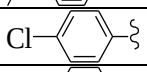
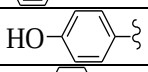
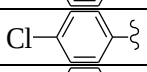
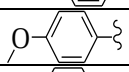
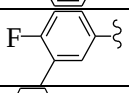
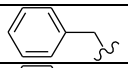
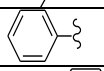
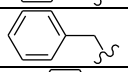
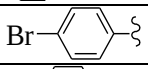
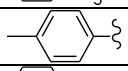
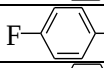
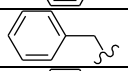
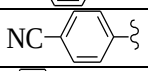
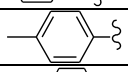
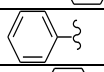
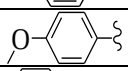
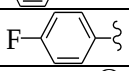
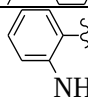
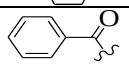
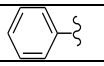
reaction rates. DMSO is reported to be the most common solvent in this synthetic way (Table 1).

Table 1: Optimum Reaction Condition

Solvent	Time (h)	Conc (M)	*T* (°C)	Yield (%)
DMSO	3	0.5	130	91

The yield obtained was higher when the reaction was carried out at a higher temperature. They investigated this synthetic strategy in the synthesis of benzimidazole analogs with different N-1 and C-2 substitutions.

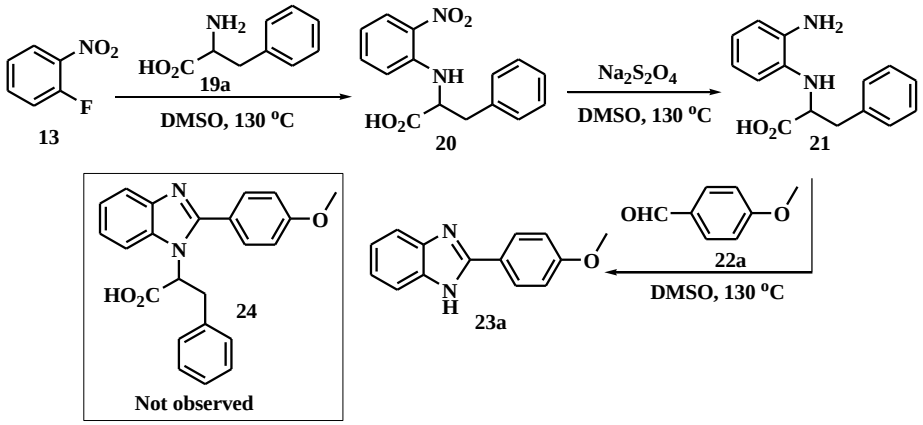
Table 2: 1, 2-Disubstituted Benzimidazoles 16 Synthesis

Entry	R^1	R^2	Yield (%)	Mp (°C)	Ref. mp (°C)
a			91	164–166	–
b			87	144–145	–
c			89	118–120	119–120
d			90	>300	–
e			81[c]	169–170	–
f			87	166–168	–
g			85	100–101	–
h			88	124–125	123–124
i			92	132–133	130–131
j			85	119–121	–
k			85	160–162	–
l			91	92–94	95–97
m			90	118–120	–
n			85	189–190	–
o			87	110–112	109–110

In this context, they decided to investigate the synthesis of amino acid intercalated benzimidazoles, as they were interested in the synthesis of benzimidazole derivatives with significant pharmacological potential. This action is based on the assumption that both the benzimidazole and amino acid moieties will be responsible for enhancing the anabolic activity of the parent compound. Initially, they attempteda simple, one-pot,

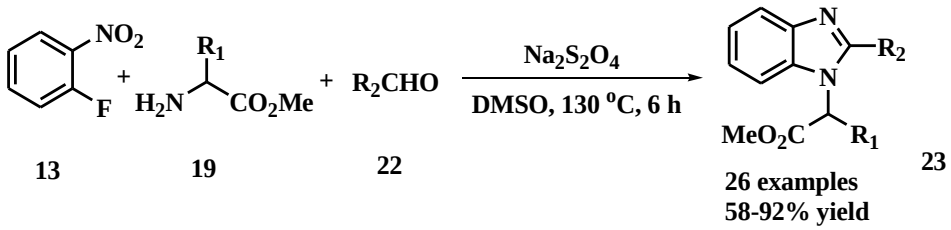
multicomponent reaction for the addition of amino acids to benzimidazoles under toxic metal free conditions(Scheme 8).

Surprisingly, instead of amino acid embedded benzimidazole **24**, unexpected 1-*H* benzimidazole **23a** was recoveredonly. This product appears to be obtained by cyclization of the aldehyde **22a** with o-phenylenediamine produced in situ. N-dealkylation of **20** or **21** in a high temperature reducing atmosphere to form O-phenylenediamine may be due to the high acidity of the reaction mixture due to the presence of amino acids and HF produced in situ.



Scheme 8: Synthetic Strategy of Amino Acid Embedded Benzimidazoles

Thus, it is a failure of the substitution-reduction-cyclization process for the direct synthesis of amino acid intercalation to benzimidazoles. They then followed the same process to obtain amino esters linked benzimidazoles using amino acid methyl esters; such compounds give more ways for structural development of amino acids.



Scheme 9: Synthesis of Amino Ester Intercalated Benzimidazole **23**

They explored the scope and generality of this reaction in the synthesis of different benzimidazole analogues by replacing N-1 and C-2 substituents.Consequently, diverse methyl ester of amino acid **19** and commercially available aldehydes**22** were reacted with 1-fluoro-2-nitrobenzene**13**(Scheme 9) in optimized conditions (Table 1). It seems that all amino ester and aldehyde are well tolerated in this conversion and the desired product is obtained in good yield. (**Figure 2**).[10]

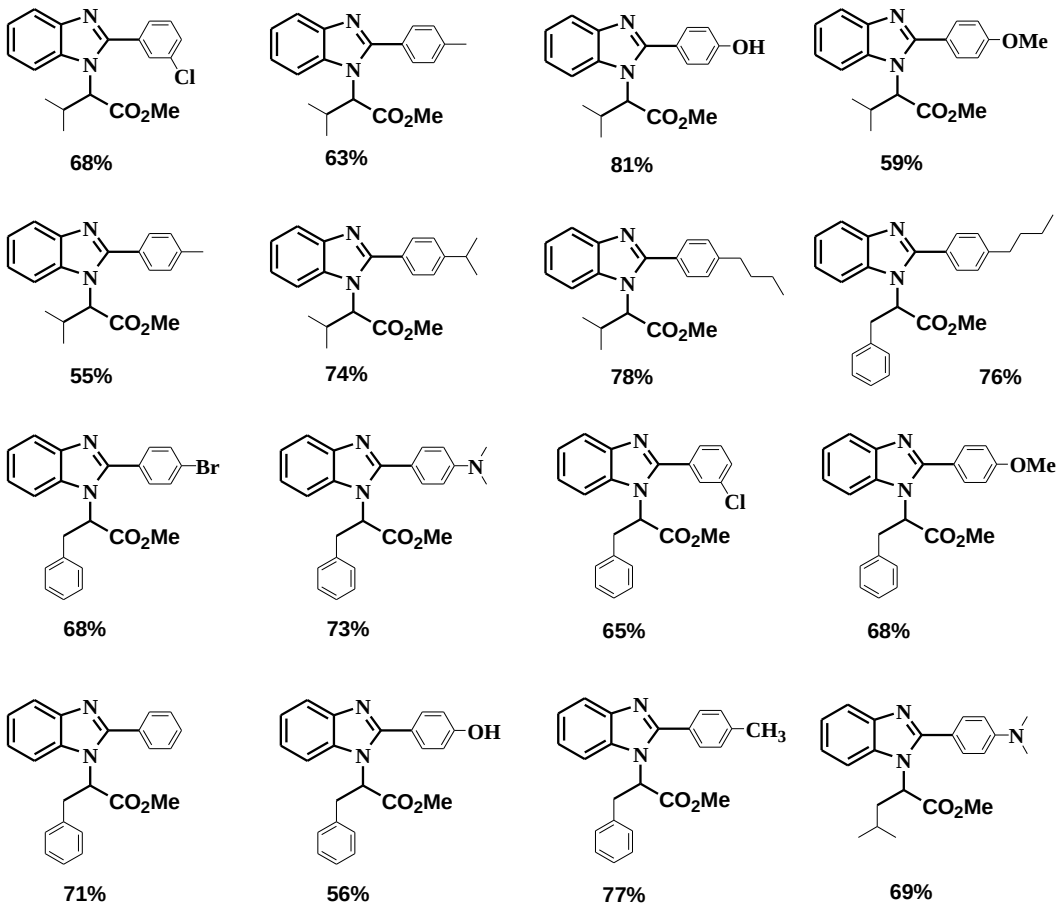
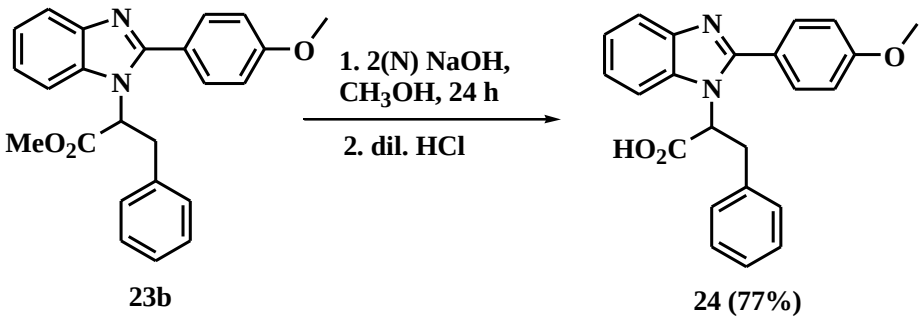


Figure 2: Reaction Scope with Different Substituents

The synthetic utility of amino ester embedded benzimidazole **23**was exemplified by further transformation shown in **Scheme 10**. When **23b** is treated with 2(N) NaOH followed by acidification with dilute HCl gave the stereochemistry preserved amino acid fused benzimidazole **24** in 77% yield.



Scheme 10: Amino Acid by Hydrolysis of Amino Ester

IV. PRESENT WORK: GREENERMCR APPROACH

Recently, we developed a simple, green one-pot sequential method for the preparation of 1,2-disubstituted 1,2-disubstituted benzimidazole derivatives under **solvent-free**and neutral conditions. Stepwise the reaction sequence is (i) activated nucleophilic substitution of 1-fluoro-2-nitrobenzenewith a primary amine, (ii) sodium dithionite induced reduction of coupled nitroarene, and (iii) coupling of an aldehydewith the corresponding diamine.

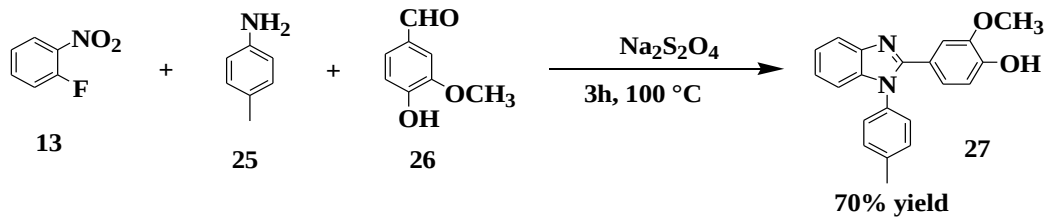
Here, we have considered the synthesis of benzimidazole **27** from 1-fluoro-2-nitrobenzene **13**,*p*-toluidine **25**and vanillin**26**(Scheme 11).

Table 2: Effect of Reaction Conditions on Thecoupling of 1-Fluoro-2-Nitrobenzene with *P*-Toluidineand Vanillin

Entry	Solvent	Time (h)	Conc (M)	*T* (°C)	Yield (%)
1	DMF	3	0.5	100	15
2	DMF	5	0.5	100	20
3	DMSO	3	0.5	100	20
4	DCM	3	0.5	−	00
5	**No solvent**	**5**	**−**	**100**	**70**
6	No solvent	5	−	70	24
7	No solvent	8	−	100	68

Curiously perceptions develop from the information in Table 2. The role of different organic solvents was examined. The yield was maximum when reaction was done on boiling water bath without solvent (entry 5).Diminish of temperature (70 °C) decreases theyield of the product (entry 6). No yield alteration was observed when the reaction mixture was stirred for longer time (entry 7).

So,1-fluoro-2-nitrobenzene **13**was treated with amine **25**at 100°C for 3h followed by treatment with sodium dithionite andvanillin**27**at the same temperature for another 2 h gave benzimidazole derivative 2-(3-methoxy-4-hydroxyphenyl)-1-(*p*-tolyl)-benzoimidazole**27** in 70% yield.

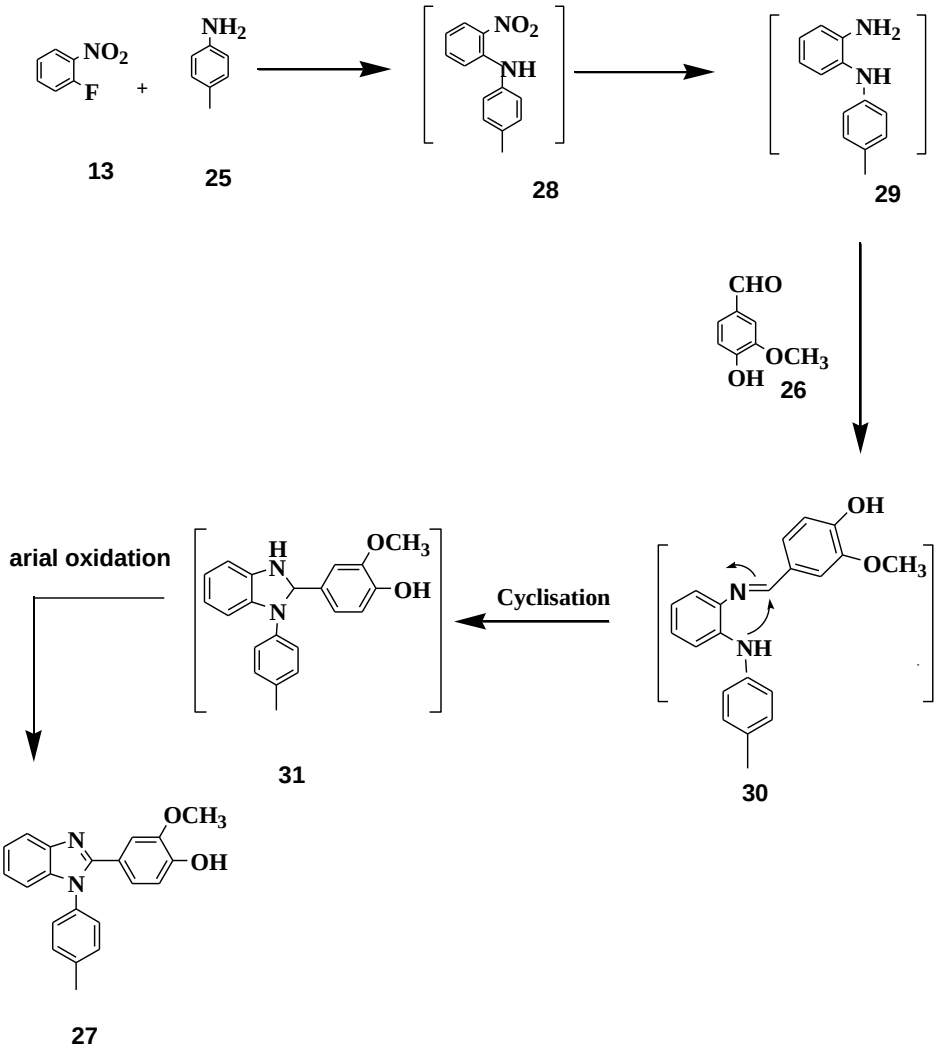


Scheme 11: Strategy towards Synthesis Of 2-(3-Methoxy-4-Hydroxyphenyl)-1-(P-Tolyl)-1H-Benzoimidazole

V. RESULT AND DISCUSSION

At coupled with *p*-toludine**25 and** 1-fluoro-2-nitrobenzene **13**by nucleophilic aromatic substitution followed by reduction of the coupled nitroarene**28** by sodium dithionite

produced the diamine intermediate **29**. When this *in situ* generated diamine intermediate **29**reacts with vanillin **26** it formed the desired 1,2-disubstituted benzimidazole **27** by sequential cyclization and aerial oxidation pathway (**Scheme 12**).



Scheme 12: A Proposed Mechanism of Formation of Compound **27**

The structure of the desired product was characterised by study of the ^{1}H NMR spectra.

1. **Green context:** The following points may be noted:

- Synthesis under neutral conditions favourable over strong acid/base-catalysed conditions that restrict functional group tolerance.
- To avoid contamination of toxic metals with the product metal free environmentally benign conditions were used.
- One-pot sequential synthesis avoids stepwise isolation process.
- Solvent free procedure and design for energy efficiency
- Inexpensive easily available starting materials were used.

VI. CONCLUSION

In conclusion, the process described here to synthesis 1,2-disubstituted benzimidazole is very easy, inexpensive and eco-friendly. The method involves the sequence of processes coupling-reduction-cyclization in one-pot under eco-friendly conditions.Our target was to make the procedure greener in environmental aspect.Slight modification of the procedure generates a great impact in green context. We have used inexpensive easily available starting materials 1-fluoro-2-nitrobenzene, p-toluidine and vanillin to synthesis 2-(3-methoxy-4-hydroxyphenyl)-1-(p-tolyl)-benzimidazole.

VII. EXPERIMENTAL

1. **Procedure for the Preparation of 2-(3-Methoxy-4-Hydroxyphenyl)-1-(P-Tolyl)-1H-Benzoimidazole (27):** A mixture of 1-fluoro-2-nitrobenzene **1** (10.0 mmol) and p-toluidine 12(10.0 mmol) in DMSO (2 mL) was stirred for 3 h at 100 °C temperature on a water bath. Sodium dithionite (12.0 mmol) and vanillin 15(12.0 mmol) was then added and heating was continued for 2 h. Water (20 mL) was added to the mixture and extracted with EtOAc (20 mL). The organic layer was washed with water (20 mL X 3) and brine (5 mL) respectively and then dried over anhydrous Na_2SO_4. Evaporation of solvent and purification by crystallization using aqueous ethanol gave the pure product.
   M.P. 120°C - 125°C
   ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.85 (s, 1H), 7.62 (d, 2H, *J* = 8.4 Hz), 7.39-7.42 (m, 2H), 7.10–7.29 (m, 5H), 6.71 (d, 2H, *J* = 8.4 Hz), 3.81 (s, 3H), 2.47 (s, 3H);

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