**Multi Component Green Approach for Synthesis of 1,2-disubstituted benzimidazole**

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ABSTRACT

An easy and inexpensive method has been developed to access 1,2-disubstituted benzimidazoles following a one-pot sequential coupling/reduction/cyclization process under metal free neutral conditions.

*Keywords****:*** Benzimidazole, Substitution, Reduction, Cyclization, One-pot synthesis, Greener Approach.

***1. INTRODUCTION***

Nitrogen-containing heterocycles are ubiquitous in nature and essential to life. They play pivotal roles in the metabolism of all living cells. Among these, substituted benzimidazoles are important pharmacophores and privileged structures in medicinal chemistry. For showing broad range of biological functions,the benzimidazole structural motif has been of great interest in many applications, especially in pharmaceuticals (Figure1)1. Compounds with benzimidazole scaffold exhibit a wide range of biological activities such as anticancer,anxiolytic, anti-inflammatory, antimicrobial, anticarcinogensand peptic ulcer agents.Benzimidazole and its derivatives are an important structural motif that are found in a wide spectrum of bio-active compounds such as nonpeptide luteinizing hormone-releasing hormone (LHRH) antagonist, lymphocyte specific kinase inhibitor, nonpeptide thrombin inhibitor and 5-lipoxygenase inhibitor.Furthermore, benzimidazoles have attracted much attention for their wide applications2 as enzyme inhibitordyes,polymers, chemo sensors and fluorescence probes. On the other hand the amino acids are becoming increasingly important in the production of pharmaceuticals and fine chemicals. They are also very important as chiral directing auxiliaries and chiral synthons in organic synthesis. They are being extensively used as key components in *β*-lactam antibiotics, fertility drugs,anticoagulants and pesticides.



**Figure 1:** Examples of drug molecules containing benzimidazole structural motif

Benzimidazole derivatives are also widely present in many therapeutic drugs such as Prilosec, Protonix (proton pump inhibitors), Atacand (hypertension) and Vermox (broad spectrum anthelmintic) as well as numerous experimental drug molecules.Therefore, it is worth mentioning that the efficient synthesis of benzimidazole scaffolds has always been a topic of interest for organic and medicinal chemists.Benzimidazoles are most commonly prepared from *ortho*-arylenediamines, which in turn, are available by *ortho*-nitration of anilines and subsequent reduction of the nitro moiety. The two principal synthetic strategies for benzimidazole formation3 are: (a) condensation of *ortho*-arylenediamines with carboxylic acids and derivatives thereof and (b) dehydrogenation of benzimidazoline intermediates generated from condensation of *ortho*-arylenediamines with aldehydes. Both the methods have some serious drawbacks. While the former requires strong acidic conditions and sometimes high reaction temperatures, the latter method requires a stoichiometric or excess oxidant. Efficient syntheses of benzimidazoles from 2-haloacetanilides,*N-*arylbenzimidamide, 2-haloarylamidine, transition-metal catalyzed aryl amination, C-H functionalization and oxidation of alcohols have recently been reported. However, each synthesis requires multistep reactions for the preparation of the starting materials.

***2.SYNTHESIS OF BENZIMIDAZOLE3***

Although a number of methods for the synthesis of 1- or 2-monosubstituted benzimidazoles have been reported, the assembly of 1,2-disubstituted benzimidazoles still encounters challenges in controlling regioisomeric selectivity, increasing efficiency, and improving generality.Most of the methods toward 1,2-disubstituted benzimidazoles such asthe condensation of carboxylic acids with N-substituted 1,2-diaminoarenes and N-arylation/alkylation reactions of 1*H*-benzimidazoles have often suffered from a limited scope and led to a mixture of two regioisomers because of the difficulty of differentiating the two N-atoms.

Alternatively, the palladium-, copper-, indium-, ruthenium-,and cobalt-catalyzed intramolecular N-arylation starting from *o*-haloanilines/ *o*-halonitrobenzene has been used. However, most of these protocols involve multistep synthetic transformations and engage a complex isolation process leading to a high cost and/or suffer from poor availability of starting materials. In some cases the uses of strong acid-catalyzed conditions limit the functional group tolerance also.

***2.1. USING IMINIUM ION AND α-AMINOALKYL4:***

 In 2016, Z. Zhang *et al.* reported an intramolecular cyclization/deprotection sequence to construct multisubstituted benzimidazoles derivatives through the combination of two distinct photocatalytic cycles, which consist of an iminium ion and a α-aminoalkyl radical pathway under visible-light photo redox conditions (Scheme1).



**Scheme 1:** Visible-light induced synthesis of multi-substituted benzimidazoles

***2.2. USING Ce (NO3)3.6H2O5:***

 In 2017, S. R. Mendes *et al.* reported the synthesis of a series of 2-substituted benzimidazoles under aerobic conditions, by simply heating 1,2-diaminobenzene and aldehydes in DMF at 80 oC, employing Ce(NO3)3.6H2O as promoter and atmospheric air as an efficient oxidant (Scheme 2). This protocol avoids the use of toxic metal catalysts, as well as additional bases and oxidants.



**Scheme 2:** Ce(NO3)3.6H2O promoted synthesis of 2-substituted benzimidazoles

***2.3. USING COMBINED Pd/C AND MONTMORILLONITE CATALYSIS6:***

 In 2012, J. Magolan*et al.* have synthesized a series of benzimidazoles from *ortho*-nitroanilines by one-pot transfer hydrogenation, condensation and dehydrogenation enabled by the concurrent use of two heterogeneous catalysts: montmorillonite-K10 and Pd/C (Scheme 3). This strategy was further employed to accomplish a five-step, three-component synthesis of an antifungal benzimidazoquinazoline by using a simple one-pot procedure.



**Scheme3:** Combined Pd/C and montmorillonite catalysis for one-pot synthesis of

Benzimidazoles

***2.4. USING COPPER-CATALYZED7****:*

 In 2011, C. Chen and co-workers successfully developed a straightforward, efficient and more sustainable copper-catalyzed method for intramolecular *N*-arylation providing the benzimidazole ring system, a valuable framework with interesting therapeutic properties (Scheme 4). The present protocol uses Cu2O in combination with a simple diamine derivative (DMEDA) as the catalyst under mild reaction conditions; furthermore, the use of a water as the solvent will render the methodology described herein economically and environmentally advantageous and of remarkable practical value for industrial applications.



**Scheme 4:** Copper-catalyzed synthesis of benzimidazole derivatives

***2.5. USING COPPER CATALYSED SYNTHESIS THROUGH C-N BOND FORMATION8****:*

 In 2011, S. Lee and co-workers have developed the synthesis of benzimidazoles by the one-pot, three-component reaction of 2-haloanilines, aldehydes and NaN3 in presence of 5 mol% of CuCl and 5 mol% of TMEDA in DMSO at 120 °C for 12 h (Scheme 5).



**Scheme 5:** Copper-catalyzed synthesis of benzimidazoles through C-N bond formation

***3. MULTICOMPONENT COUPLING REACTION (MCR) APPROACH TOWARDS BENZIMIDAZOLE SYNTHESIS9:***

In 2011, we have developed a simple one-pot multicomponent reaction sequence to access these ring systems under metal free neutral conditions (Scheme 6).



**Scheme 6: S**ynthesis of benzimidazoles under metal free condition

The synthetic approach involves (i) coupling of a primary amine **14** with 1-fluoro-2-nitrobenzene **13**, by nucleophilic aromatic substitution, (ii) reduction of the coupled nitroarene **17** by sodium dithionite and (iii) cyclisation of the corresponding diamine **18**using an aldehyde **15**(Scheme 7**).**



**Scheme 7**: Strategy towards synthesis of benzimidazoles

**What is Multicomponent Coupling Reaction (MCR)?**

*MCR is a method in which three or more components are combined in a single reaction vessel to give a product that incorporates substantial portions of all the components.*

***Advatages of MCRs***

**Intrinsic aspect**

Supirior atom economy

Atom utilization

Selectivity

Reduces by-products

**Extrinsic aspects**

Simpler procedure and equipments

Reduction of cost, time and energy

We had done the pentannulation reaction in different reaction conditions. Reaction temperature and solvents were found to have dramatic effects on the reaction. DMSO was reported as the best solvent in this synthetic strategy(Table 1).

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

**Table 1:** Optimum reaction condition

Higher yield was obtained when the reaction was performed at higher temperature. They explored this reaction in the synthesis benzimidazole analogues (Table 2) varying the substituent at N-1 and C-2.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Entry | R1 | R2 | Yieldb (%) | Mp (°C) | Ref. mp (°C) |
| a |  |  | 91 | 164–166 | – |
| b |  |  | 87 | 144–145 | – |
| c |  |  | 89 | 118–120 | 119–120 |
| d |  |  | 90 | >300 | – |
| e |  |  | 81c | 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 |

**Table 2** Synthesis of 1,2-disubstituted benzimidazoles **16**

In this context, because of their interest towards the synthesis of benzimidazole derivatives of potential pharmacological importance they decided to explore the synthesis of amino acid embedded benzimidazoles. This initiative was based on the assumption that both the benzimidazole and the amino acid moieties would be responsible for enhancing the anabolic activity of the individual parent compounds.

Initially, they attempted a simple one-pot multicomponent reaction sequence to access amino acid embedded benzimidazoles under metal-free conditions (Scheme 8).

Surprisingly, instead of amino acid embedded benzimidazole **24**, an unusual 1-*H* benzimidazole **23a** was obtained exclusively. This product is most likely derived from the cyclization of aldehyde **22a** with the *in situ* generated *o*-phenylenediamine. Probably the high acidity of the reaction mixture due to the presence of amino acids as well as the *in situ* generated HF causes *N*-dealkylation of either **20** or **21** to form *o*-phenylenediamine in a reducing atmosphere at high temperature.



**Scheme 8:** Strategy towards synthesis of amino acid embedded benzimidazoles

 So, this was a general failure of the substitution/reduction/cyclization process for synthesis of amino acid embedded benzimidazoles directly. Then they followed the same procedure using methyl ester of amino acid to get the amino ester embedded benzimidazole because such compounds provide a further avenue for structural elaboration of amino acids.



**Scheme 9:** Synthesis of amino ester embedded benzimidazoles **23**

They explored the scope and generality of this reaction in the synthesis of different analogues varying the substituent at N-1 and C-2. Accordingly, a variety of methyl ester of amino acid **19** and commercially available aldehydes **22** were reacted with 1-fluoro-2-nitrobenzene**13** (Scheme 9) under the optimized conditions (Table 1). As evident, all the amino ester and aldehyde participated well in this substitution/reduction/cyclization reaction affording the desired products in good yields (**Figure 2**).10



**Figure 2:** Substrate Scope of the Reaction

The synthetic utility of amino ester embedded benzimidazole **23**was exemplified by further transformation shown in **Scheme 10**. Treatment of **23b** with 2(N) NaOH followed by acidification with dilute HCl resulted in the formation of amino acid embedded benzimidazole **24** in 77% yield with retention of stereochemistry.



**Scheme 10:** Conversion of amino ester to amino acid

***4. PRESENT WORK: MORE GREEN MCR APPROACH***

Recently, we have developed a straightforward green and more sustainable one-pot sequential procedure of 1,2-disubstituted benzimidazole derivatives under **solvent-free** neutral conditions(Scheme 1). The synthetic approach involves (i) coupling of a primary amine with 1-fluoro-2-nitrobenzene, by nucleophilic aromatic substitution, (ii) reduction of the coupled nitroarene by sodium dithionite and (iii) cyclisation of the corresponding diamineusing an aldehyde.

we have considered the coupling of 1-fluoro-2-nitrobenzene **13** with *p*-toludine **25**and vanillin**26**(Scheme 11).

**Table 2:**Effect of reaction conditions on thecoupling of 1-fluoro-2-nitrobenzene with *p*-toludineand 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 |

Interesting observations emerge from the data in Table 2. The effect of various organic solvents was checked. The yield was maximum when reaction was done on boiling water bath without solvent (entry 5).Decrease of reaction temperature (70 °C) decreases the product yield (entry 6). No change in yield was observed when the reaction mixture was allowed to stir for a longer time (entry 7).

So, exposure of amine **25** to 1-fluoro-2-nitrobenzene **13** at 100°C for 3 h followed by treatment with vanillin**27** and sodiumdithionite at 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 of2-(3-methoxy-4-hydroxyphenyl)-1-( *p*-tolyl)-1H-benzoimidazole

***5. 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 cyclized product was determined by study of the 1H NMR spectroscopic data.

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

(a) Synthesis under neutral conditions favourable over strong acid-catalysed conditions that limit functional group tolerance.

(b) Metal free conditions are environmentally benign because transition metal-catalysed methods pose a threat of contamination of toxic metals with the product.

(c) One-pot sequential synthesis avoid stepwise isolation process.

(d) Solvent free procedure and design for energy efficiency

(e) Inexpensive easily available starting materials were used.

***6. CONCLUSION***

In conclusion, a straightforward, efficient and more sustainable metal-free one-pot sequential synthesis of 1,2-disubstituted benzimidazole derivatives has been described. The protocol involves coupling of a primary amine with 1-fluoro-2-nitrobenzene/reduction of the coupled nitroarene by sodium dithionite/cyclisation of the corresponding diamine using an aldehyde. And then our target was to make the procedure more 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-toludine and vanillin to synthesis 2-(3-methoxy-4-hydroxyphenyl)-1-(p-tolyl)-benzimidazole.

***7. EXPERIMENTAL***

**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 Na2SO4. Evaporation of solvent and purification by crystallization using aqueous ethanol gave the pure product.

M.P. 120°C - 125°C

**1H NMR (300 MHz, DMSO-d6): *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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