SYNTHESIS OF 2-(4-HYDROXYPHENYL)-1-(P-TOLYL)-BENZIMIDAZOLE UNDER SOLVENT-FREE NEUTRAL CONDITION

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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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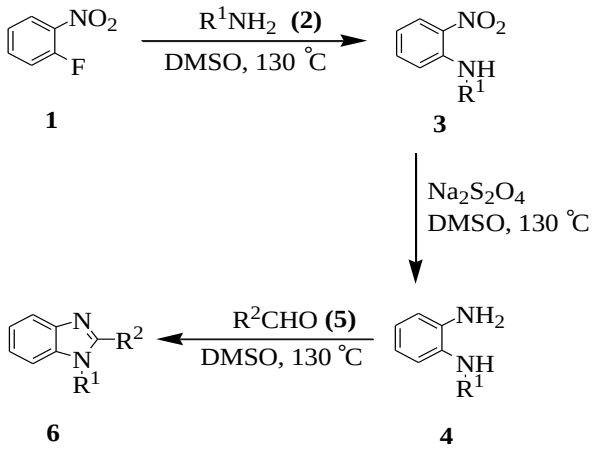
Substituted benzimidazole are very important compounds because of their pharmacological and biological activities[1]. 1,2-disubstituted benzimidazoles represent an important branch of this class. These structures were reported as valuable biologically active structures, such as specific angiotensin II receptor type 1 selective antagonists, or hepatitis C virus NS5B polymerase inhibitors. In addition, they exhibit several other pharmacological activities including anticancer, anxiolytic, anti-inflammatory, and antimicrobial activities.

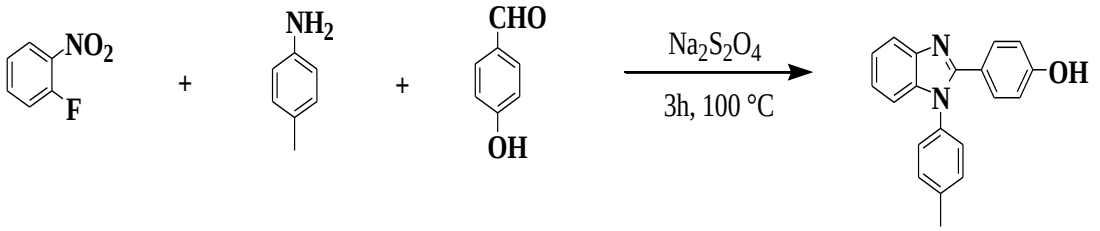
There are numerous methods for the synthesis of 1- or 2-monosubstituted benzimidazoles. Still the assembly of 1,2-disubstituted benzimidazoles encounters challenges in controlling regioisomeric selectivity, increasing efficiency, and improving generality. Most of the methods[2,3] toward 1,2-disubstituted benzimidazole derivatives such as the condensation of N-substituted 1,2-diaminoarenes with carboxylic acids 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 problem 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. In addition, the employed metals are not environmentally friendly and not attractive for commercial adoption due to low activity as catalyst and the generation of corrosive waste. These drawbacks prompted us to investigate a more practical access to the 1,2-disubstituted benzimidazole scaffold.

Here in, we are going to describe a green procedure to access benzimidazole ring system under metal free neutral conditions (Scheme 1)[4,5]. The synthetic approach involves (i) coupling of a primary amine **2** with 1-fluoro-2-nitrobenzene **1**, by nucleophilic aromatic substitution, (ii) reduction of the coupled nitroarene **3** by sodium dithionite and (iii) cyclisation of the corresponding diamine **4** using an aldehyde **5**.



Scheme 1. Strategy towards synthesis of benzimidazoles.

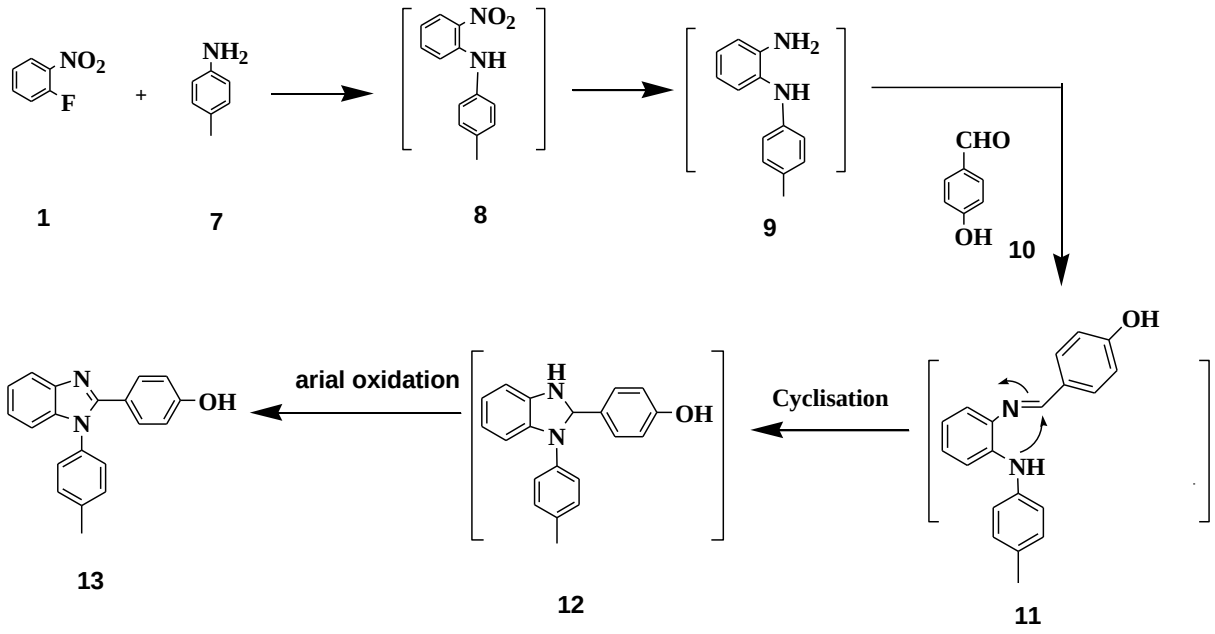
we have considered the coupling of 1-fluoro-2-nitrobenzene **1** with *p-toludine***7**and *4-hydroxy phenol* (**Scheme 2**). Thus, exposure of amine **2a** to 1-fluoro-2-nitrobenzene **1** in solid state at 100°C for 3 h followed by treatment with vanillin and sodium dithionite at same temperature for another 1 h gave benzimidazole derivative 2-(4-hydroxyphenyl)-1-(*p*-tolyl)-benzimidazole in 70% yield.



1-fluoro-2-nitrobenzene ***p*-toludine** ***p*-hydroxy benzaldehyde** **2-(4-hydroxyphenyl)-1-(p-tolyl)-benzoimidazole**

Scheme 2: Strategy towards synthesis of 2-(4-hydroxyphenyl)-1-(p-tolyl)-benzimidazole

At first coupled with *p*-toluidine 7 and 1-fluoro-2-nitrobenzene 1 by nucleophilic aromatic substitution followed by reduction of the coupled nitroarene by sodium dithionite produced the diamine intermediate 9. When this *in situ* generated diamine intermediate 9 reacts with vanillin 10 it formed the desired benzimidazoles 13 by sequential cyclization and aerial oxidation pathway (Scheme 5.3).



Scheme 3: A proposed mechanism of formation of compound 1**3**

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.
(e) Inexpensive easily available starting materials were used.

Our work focuses on the successful execution of the One-pot sequential procedure under metal free conditions developed by A Pramanik and co-workers for synthesis of 2-(4-hydroxyphenyl)-1-(p-tolyl)-benzimidazole. Slight modification of the procedure generates a great impact in green context. In addition, we have used inexpensive easily available starting materials to synthesis 2-(4-hydroxyphenyl)-1-(p-tolyl)-benzimidazole which is completely new in this procedure.

EXPERIMENTAL

Procedure for the preparation of 2-(4-hydroxyphenyl)-1-(p-tolyl)-benzimidazole

A mixture of 1-fluoro-2-nitrobenzene (10.0 mmol) and p-toluidine (10.0 mmol) in DMSO (2 mL) was stirred for 5 h at 100 °C temperature on a water bath. Sodium dithionite (12.0 mmol) and 4-hydroxy phenol (12.0 mmol) was then added and heating was continued for 3 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 products. M.P. 112°C - 115°C

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.97 (s, 1H), 7.86 (d, 1H, *J* = 8.4 Hz), 7.52-7.61 (m, 3H), 7.38–7.12 (m, 7H), 6.98 (d, 2H, *J* = 8.4 Hz), 2.41 (s, 3H);

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