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One-pot synthesis of benzimidazole using DMF as a multitasking reagent in presence $CuFe_2O_4$ as catalyst

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ABSTRACT

One pot synthesis of benzimidazole from *o*-nitroaniline was achieved by using $CuFe_2O_4$ as a catalyst. It comprises the reduction of *o*-nitroaniline followed by cyclization, without using an external H_2 source. The thermal decomposition of DMF in situ generates CO, which undergo water gas shift reaction (WGSR) in the presence of $CuFe_2O_4$ to produce hydrogen. It reduces $-NO_2$ (nitroaniline) to $-NH_2$ (*o*-phenylenediamine, OPD). The further cyclisation of OPD to benzimidazole was done by using DMF as a C1 source, in the presence of magnetically separable $CuFe_2O_4$ as catalyst. This is the first example of its kind being reported here. The catalyst was prepared by a simple hydrothermal method, with an environmentally benign starting material. $CuFe_2O_4$ is cheap and reusable having very low toxicity. This is an economical synthetic protocol for benzimidazole from *o*-nitroaniline with 100% conversion in 12 h with 97.5% selectivity. A variety of *o*-nitroaniline substrates were studied using the protocol with excellent conversion and selectivity in each case.

1. Introduction

Synthesis of heterocyclic compounds is an important motif in organic synthesis. Benzimidazole derivatives are the building blocks of bioactive heterocyclic compounds and have a great medicinal and pharmaceutical value. They exhibit wide therapeutic applications in biological and clinical operations [1,2]. Benzimidazole derivatives are naturally occurring isostere of nucleotides [3] which show therapeutic activity towards HIV [4] and are anticancer [5], anti-inflammatories [6], antibacterial [1], antifungal [7], anti-histaminic [8], antioxidant [9], antihypertensives [10], and anticoagulant agents [11]. Some common drugs derived from benzimidazole are bendamustine, omeprazole, esomeprazole, astemizole, candesartan, albendazole, candesartan and enviradene, etc [12]. (Scheme 1). Hence, efficient and economical production of benzimidazole should be on high priority.

In previous reports, the synthesis of benzimidazole is claimed by using a variety of methods. The most well-known method is the coupling of *o*-phenylenediamine (OPD) with an excess of formic acid, which serves as a reactant and solvent [13]. Conventionally, it was also synthesized by cyclization of OPD using different carbon sources like orthoformates [14–16], amide [17], DMF [18] and carbon dioxide (CO_2) [19,20]. A new protocol has been developed for the synthesis of benzimidazole from *o*-nitroaniline. It includes two steps; the first is the reduction of *o*-nitroaniline to OPD and the second is cyclization of OPD to benzimidazole. A one-pot synthetic method from *o*-nitroaniline is reported in the literature using microwave irradiation and $SnCl_2$ catalyst [21] and ultra-sonication in the presence of Fe powder as catalyst [22] with common starting materials such as carboxylic acids. It is also synthesized by transfer hydrogenation over Pd/C and K-10 clay (co-catalyst) using aldehyde as a carbon source [23]. Hou et al. [24] have used H_2 for reduction and CO_2 as a necessary carbon source using Au/TiO_2 as a catalyst. Sun et al. [25] reported supercritical methanol as a source of necessary carbon at 250 °C using Cu-PMO as a catalyst (Scheme 2).

These methods have common drawbacks such as requirement of costly coupling reagents, high working temperature and generation of huge waste. To this end, there is a need to develop an efficient synthetic method for the synthesis of benzimidazole.

Reduction of $-NO_2$ to $-NH_2$ is a key transformation in heterocyclic chemistry [26]. In this regard reports are available using different H_2 sources such as molecular H_2 [27,28], $NaBH_4$ [29], NH_2-NH_2 [30], hydrosilane [31], formic acid [32], etc. in combination with precious metal catalysts. Beller et al. [33–35] studied a process based on in-situ synthesized H_2 from water gas shift reaction (WGSR) with carbon monoxide (CO). This hydrogen source is the best way for hydrogenation reaction because handling and storage of hydrogen is a much difficult task. However, use of non-toxic and inexpensive reagent like DMF acting as a liquid H_2 carrier would be interesting [36].

Yu et al. [37] reported that mixture of DMF and water in the presence of platinum complexes gives H_2. Also, other few reports are also

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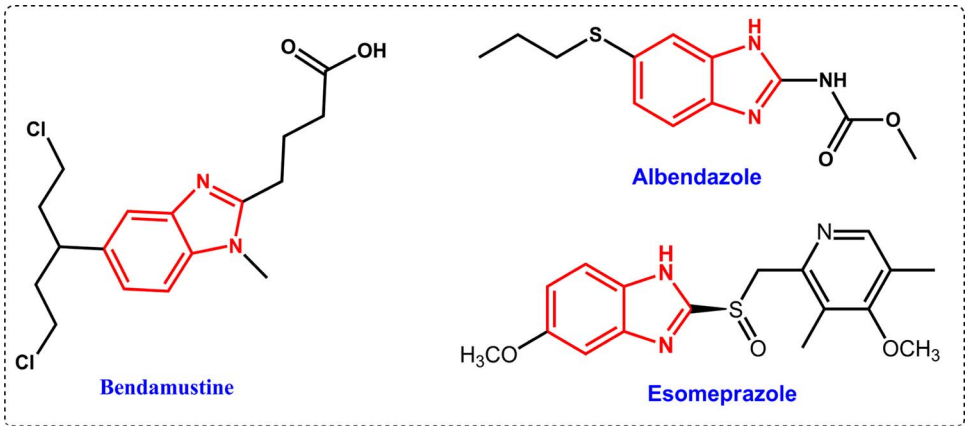
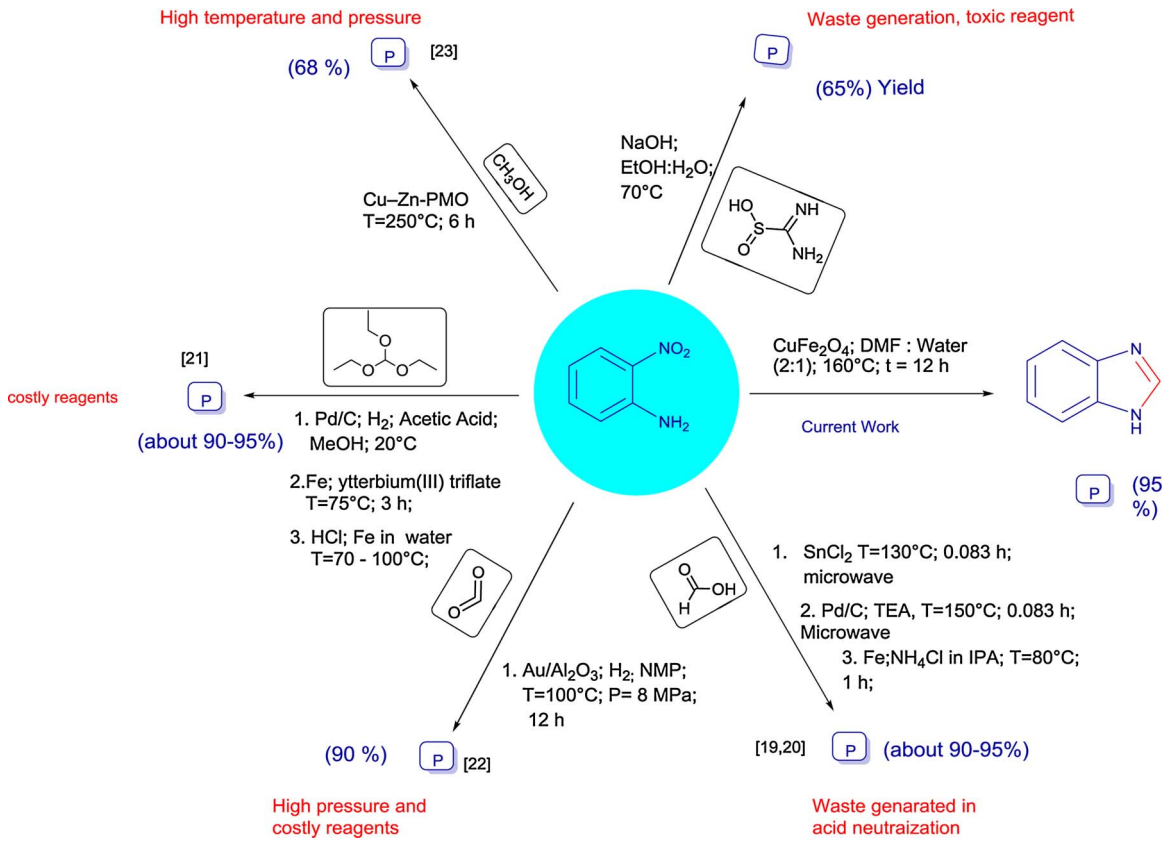


Scheme 1. Common drugs containing benzimidazole as a building block.



Scheme 2. Examples of synthesis of benzimidazole from different sources (Prior art).

published in this regard [36–39]. DMF is an easily available starting material, which serves as a source of −CO [40], −CN [41], $-NMe_2$ [42], −Me [43], and −CHO [44,45] depending upon reaction protocols and conditions. We have synthesized CO_2 mediated benzimidazole using DMF as a carbon source for cyclization of OPD [20].

Herein, we propose a simple and cost effective, one pot synthesis of benzimidazole from *o*-nitroaniline using magnetically separable $CuFe_2O_4$ catalyst. DMF in the presence of water decomposes to CO and dimethylamine. The in-situ generated 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 $-NH_2$ (OPD) in the presence of $CuFe_2O_4$ and further, OPD is cyclized to give benzimidazole using DMF as a necessary carbon source. The formation of OPD as an intermediate was confirmed by GC–MS and NMR. To our knowledge this type one pot reaction has not been not reported in the literature (Scheme 3).

$CuFe_2O_4$ (nanospheres) were prepared by a well-known hydrothermal method using sodium acetate as a capping reagent [46,47]. It forms an inverse spinal (AB_2O_4) type structure. Cu^{2+} occupies the octahedral site, whereas half of Fe^{3+} occupies tetrahedral sites. It can be expressed as $(B^{III})^{tet}(A^{II}B^{III})^{oct}O_4$. It is widely used as a catalyst for WGSR [48]. The fresh and reused $CuFe_2O_4$ catalysts were characterized by different analytical techniques.

2. Experimental section

2.1. Chemicals

Ethylene glycol, methanol, sodium acetate, $CuCl_2{\cdot}2H_2O$, $FeCl_3$, $NiCl_2{\cdot}6H_2O$, $MnCl_2{\cdot}4H_2O$, $CoCl_2{\cdot}6H_2O$, $NiCl_2$ (anhydrous) and other chemicals were procured from Alfa-Aesar, Mumbai, India, and 2-nitrophenol and substituted nitrophenols from Sigma-Aldrich. All