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One Pot Reductive Synthesis of Benzimidazole Derivatives from 2-Nitro Aniline and Aromatic Aldehydes Using Zn/$NaHSO_3$ in Water Medium

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ABSTRACT

Small amount of Zn dust and $NaHSO_3$ was utilized to efficiently synthesize benzimidazole derivatives via one pot reductive cyclocondensation process in water medium at 100°C temperature. Very good to excellent yields in reasonably short reaction times, high atom economy and usage of readily available starting material, operational simplicity and easy workup are the fundamental features of this protocol.

HIGHLIGHT

- One potreaction
- Chemoselective reductive cyclisation reaction.
- Aqueous medium.
- Shorter reaction time.
- Easy reaction set-up.
- Inexpensive, easily available reagent, easily separable by simple filtration.
- Mild reaction condition.

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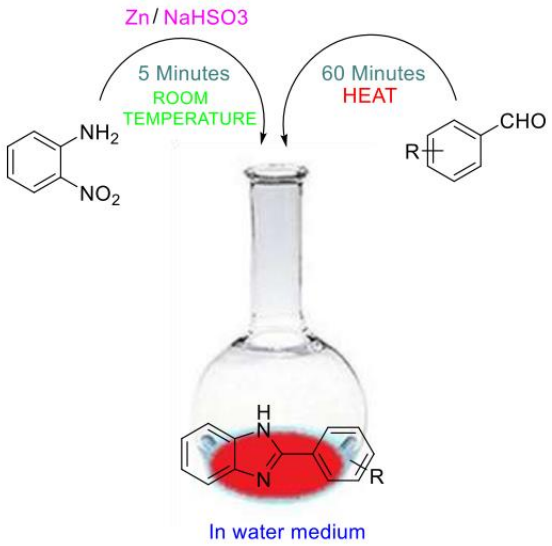
GRAPHICAL ABSTRACT



Introduction

Substituted benzimidazoles display beneficial biological properties such as antihypertensives, antivirals, antifungals, anticancers, and antihistaminics[1]. Furthermore, compounds belonging to this class have been employed as versatile building blocks of anthelmintics[2], proton pump inhibitors[3], and a host of pharmaceutical compounds [4]. A series of compounds with benzimidazole motifs have been used in the textile industry as wetting, emulsifying, foaming, or softening agents or as dispersants for use in dyeing.

As a consequence, a number of researchers have set their goal to synthesize benzimidazoles derivatives. Historically, the first benzimidazole was prepared in 1872 by Hoebrecker. To overcome the drawbacks of classical methods, the most common approaches to benzimidazoles are the combination of 1, 2-phenylinediamine with aldehyde [5-26], carboxylic acid [27-31] and ester [32-33] under different catalytic conditions.

Most of the protocols, however, suffer from drawbacks such as harsh reaction conditions, high temperature, strongly acidic / basic condition, prolonged reaction time, use of homogeneous catalyst, low yield and suffer from rapid loss of catalytic activity. Although the acceptable yield of benzimidazoles has been reported in most of the protocols where either toxic metal catalyst or costly reagents were used, people had to suffer handling tedious reaction conditions and work up process. To avoid these limitations, it is imperative to develop a high yielding greener, simple, cost effective and catalyst free efficient method for its synthesis with a broad range of substrate applicability.

Although 2-nitroaniline appears to be a potential precursor for a possible route to benzimidazole derivatives but except very few [34-36] reports, people have not yet explored its applicability.

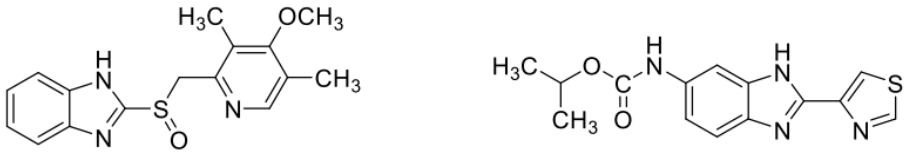
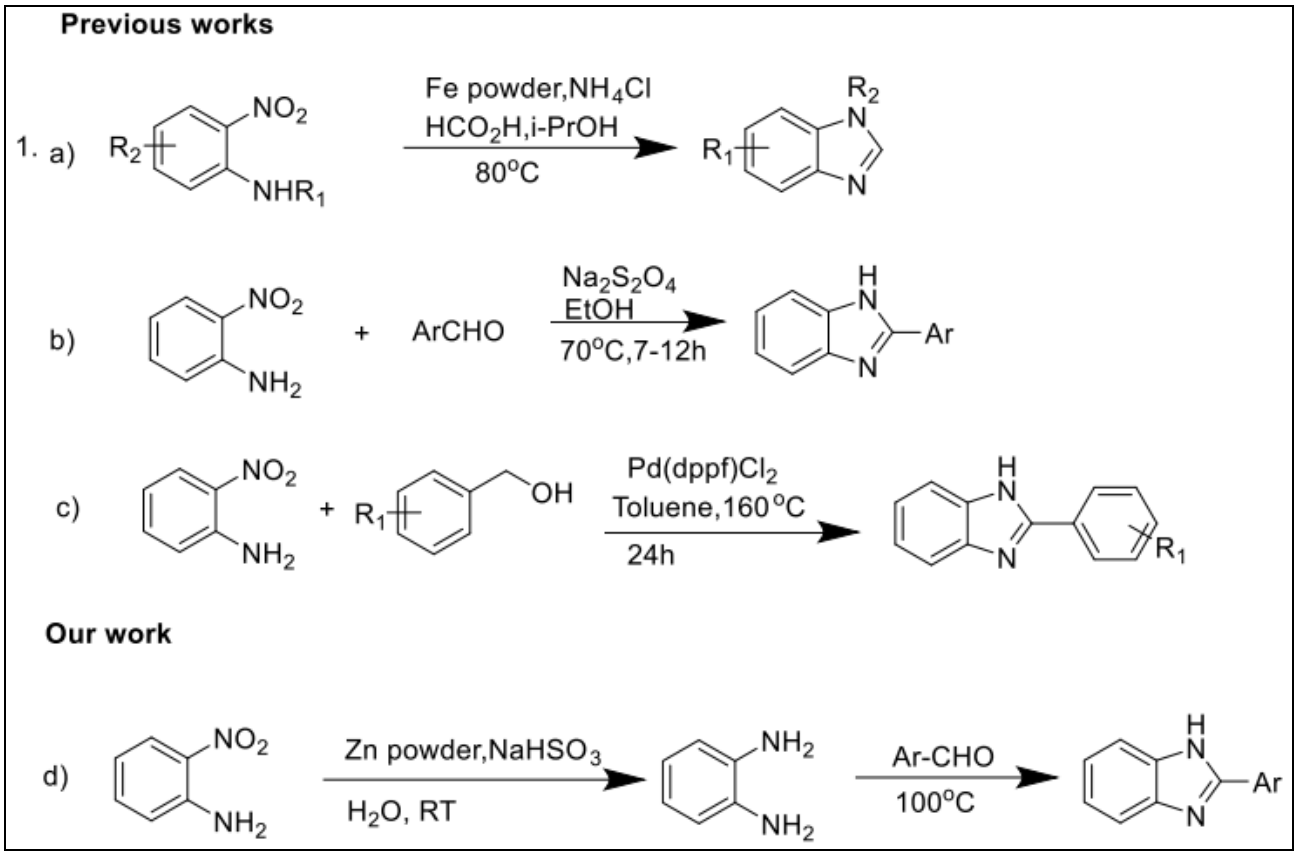


Figure 1: Examples of some bioactive benzimidazole derivatives

Based on the above reports, it seems necessary to develop an easy, cost-efficient and simple method for the preparation of these derivatives which meet the present demand for sustainable development. Keeping these issues in mind, we here reported a simple and mild one-pot method for the synthesis of 2-substituted benzimidazoles (scheme 1, d) from 2-nitroanilines by reductive cyclocondensation with a combination of suitable metal, Zn and metal salt $NaHSO_3$ at 100°C in water. $NaHSO_3$ is a non-hazardous, easily available, inexpensive weakly acidic species having pKa value 6.97, which helps to trigger the reaction in the presence of Zn. Its adduct formation ability with the aldehydes may contribute to cyclocondensation in the present protocol.



Scheme 1: Comparison of previous work and our work for the synthesis of benzimidazole derivatives.

Experimental Materials

Chemicals

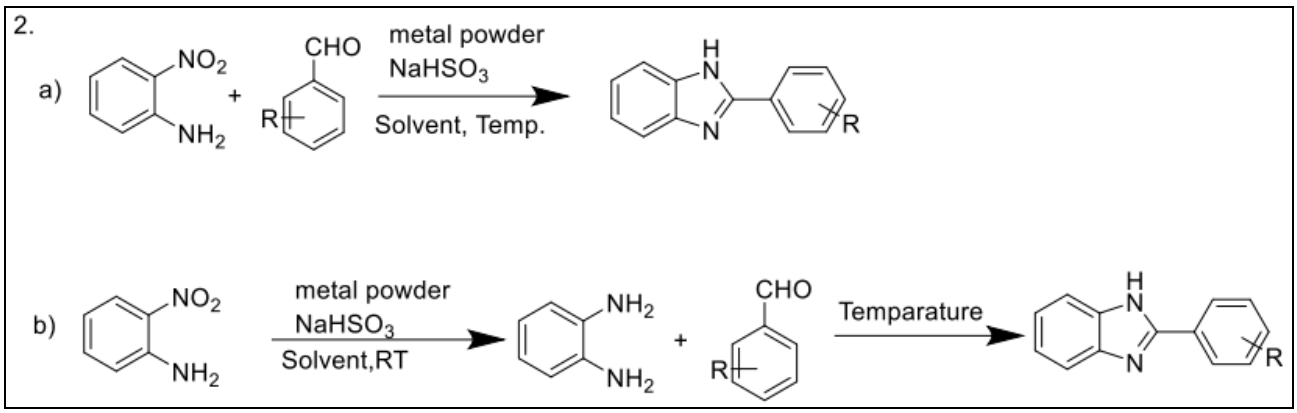
All the chemicals and solvents used in the study were purchased from commercial sources of Sigma Aldrich and SD Fine chemical company and were used without further purification unless stated. The organic solvents used were of analytical or spectroscopic grade. Before using, the solvents were dried and freshly distilled using the standard procedures whenever anhydrous solvents were required.

General Experimental Procedure

In a round bottom flask 2-nitro aniline (1 mmol), Zn powder (3 mmol), $NaHSO_3$ (6 mmol) in 20 mL water at room temperature was stirred on a magnetic stirrer. After 10 minutes, aromatic aldehyde was added into it and at 100 ^oC the mixture was stirred on a magnetic stirrer for 30 minutes. One cotton ball was present on the mouth of the round bottom flask during the process of reaction. The progress of the reaction was monitored by TLC. After completion of the reaction, the metallic part was filtered off. The filtrate was poured into 100 mL ice cold water, extracted with ethyl acetate, and washed several times with water. Evaporation of solvent followed column chromatography over basic alumina using petroleum ether/ethyl acetate (3:1) as eluent to afford the pure benzimidazole derivatives.

Results and Discussion

The general scheme and reaction are shown in scheme 2(a) and 2(b). The compound obtained were monitored by TLC and separated by column chromatography.



Scheme 2: Two different plan for the synthesis of benzimidazole derivatives.

Table1. [a]Reaction (Scheme-2a) condition optimization.

Entry	Time (min.)	Temperature (^oC)	Additive (3 mmol)	Yield of diamine	Yield of Benzimidazole
1	10	RT	$NaHSO_3$	70	Nil
2	10	60	$NaHSO_3$	44	Nil
3	10	80	$NaHSO_3$	25	Nil
4	10	RT	-	Nil	Nil

[a]Reaction of *o*-nitrobenzaldehyde (1 mmol), Fe (3mmol), in water on magnetic stirrer.

Table2. [a]Reaction (Scheme-2b) conditions optimization.

Entry	Metal	Solvent	Time(min.)	Temperature(°C)	Yield (%)[b]
1	Fe	DMF	60	100	68
2	Fe	DMSO	60	100	60
3	Fe	Toluene	60	100	56
4	Fe	H_2O	60	100	80
5	Fe	-	60	100	Nil
6	Cu	H_2O	60	100	75
7	Zn	H_2O	60	100	94
8	-	H_2O	60	100	Nil
9	Zn	H_2O	60	RT	Nil
10	Zn	H_2O	60	80	50
11	Zn	H_2O	60	60	Nil
12	Zn	H_2O	60	40	Nil
13	Zn	H_2O	90	100	95
14	Zn	H_2O	45	100	87
15	Zn	H_2O	120	100	94

[a]Reaction of o-nitrobenzaldehyde (1 mmol), Zn (3mmol), $NaHSO_3$ (6 mmol) in water on magnetic stirrer. [b]Isolated yield of benzimidazole

Table 3. [a]Optimization of amount of Zn and $NaHSO_3$

Entry	Zn (mmol)	$NaHSO_3$ (mmol)	Time (min)	Yield (%)[b]
1	3	3	60	54
2	3	4	60	62
3	3	5	60	82
4	3	6	60	94
5	3	7	60	94
6	2	6	60	75

[a]Reaction of *o*-nitrobenzaldehyde (1mmol), Zn (2-3 mmol), $NaHSO_3$ (4-7 mmol) in water on magnetic stirrer at 100°C. [b]Isolated yield.

To screen the reaction, 2-nitroaniline and benzaldehyde were selected as model substrates for intended transfiguration. Initially, we performed the reaction of *o*-nitroaniline with benzaldehyde in water at room temperature for 1h on a magnetic stirrer in presence of the combination of Fe powder and sodium bisulphite. The reaction yielded only the diamine (o-phenylenediamine). The yield of diamine decreases with a rise in temperature and benzimidazole was undetected (Table1, scheme-2a). It was also tried (scheme-2a) without using $NaHSO_3$ (Table 1, entry 4), but it failed to produce the diamine even at a trace amount. Thus, it is obvious that, as a hydrogen ion's source, $NaHSO_3$ plays a vital role to reduce nitro to amine. With this experimental data we followed our scheme 2b. In this process *o*-nitroaniline was reduced to 1, 2-diamine with Zn and $NaHSO_3$ in presence of water at room temperature and the process was completed within 5 minutes.

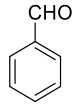
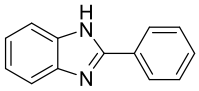
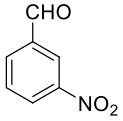
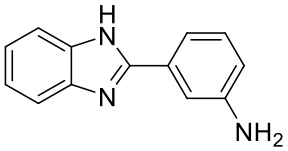
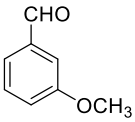
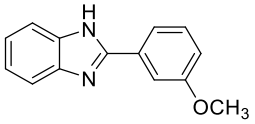
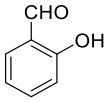
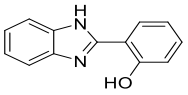
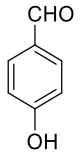
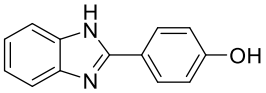
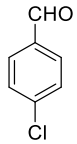
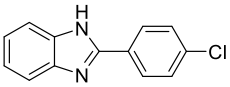
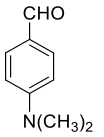
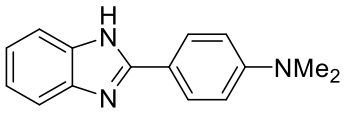
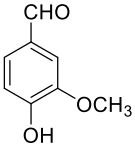
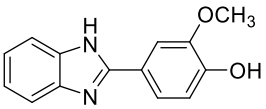
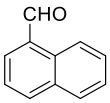
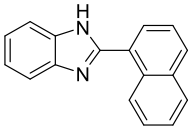
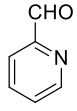
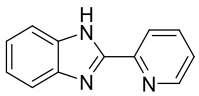
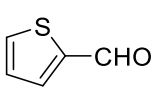
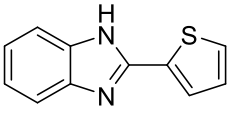
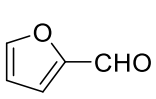
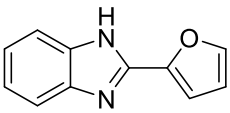
It was followed by the addition of benzaldehyde with continuous stirring at 100 ^oC. As a solvent, water was first screened (Scheme 2b, Table 2, entry 4), and very surprisingly no product was isolated in its absence (Table 2, entry 5). Further, as the most easily available and most significant, its green nature has really enriched the objective of the present investigation.

The presence of metal is the necessary requirement for the initial reduction of the nitro compound (Table 2, entry 8) and in comparison to Fe and Cu, Zn is estimable in terms of yield of the product and the time of completion of reaction (Table 2, entries 4, 6, 7). We also tried the scheme at different temperature; finally, at 100 ^oC temperature the desired product, i.e. benzimidazole, was isolated as a single compound (Table 2, entry 7). Further, we optimized the amount of Zn and $NaHSO_3$ required (Table 3).

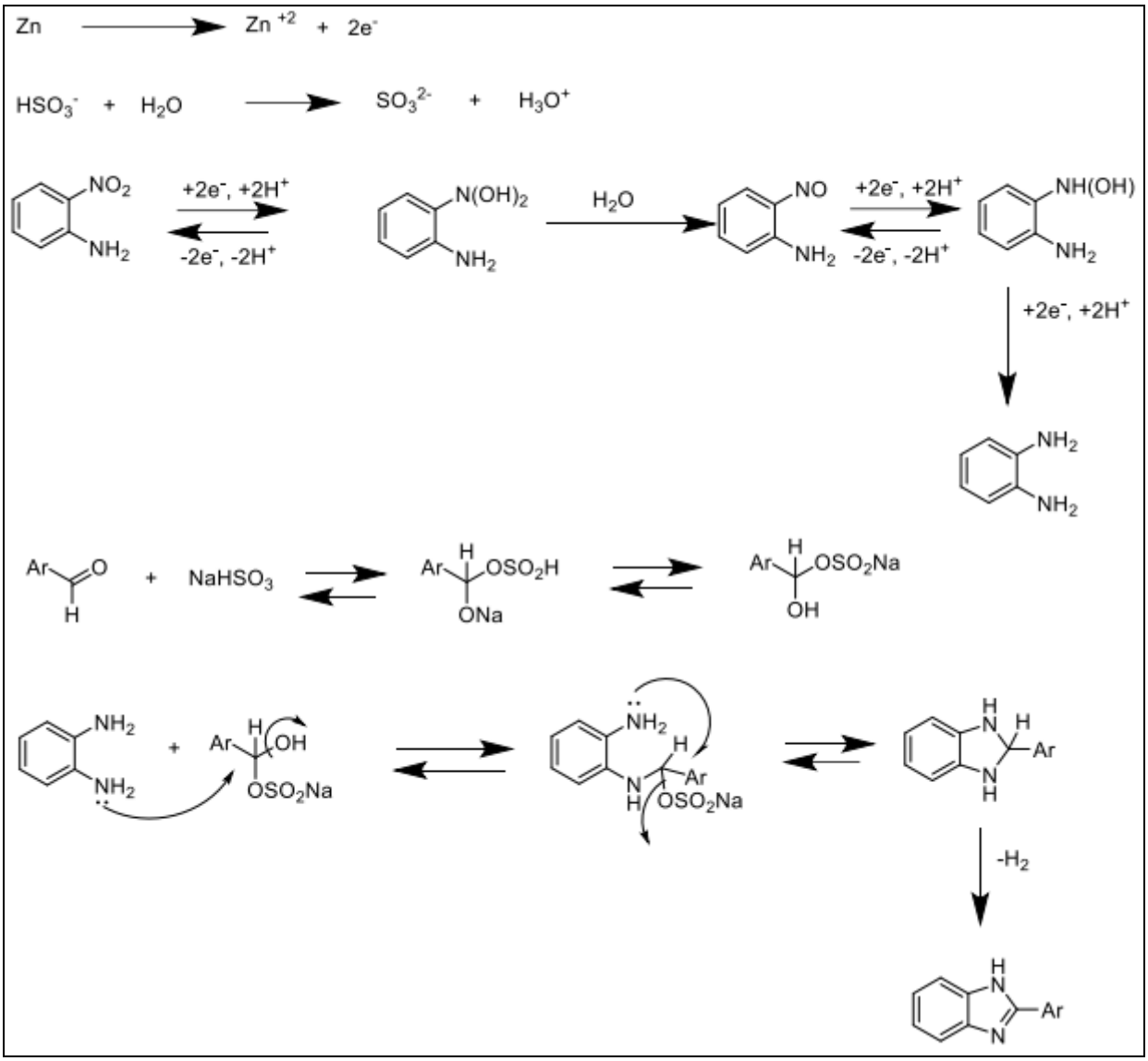
Further investigation towards the optimization of the process revealed that a 3 mmol Zn and 6 mmol $NaHSO_3$, (Table 3) under atmospheric pressure at 100^oC yielded the best result to produce the desired benzimidazole in 1h (compared with Table 2, entries 7, 14, 15). This procedure was followed for all of the reactions listed in Table (4). Staggering part of our reaction was chemoselective reduction of nitro to amine. We really enthralled and exhilarated on observing Table 4 entry 3, 4, 5, 6, 7, 8 that reducible groups remain intact after completion of the reaction. The reaction took place smoothly to produce corresponding benzimidazole in moderate to high yields.

From the above observation, we can propose a possible mechanism and tentative intermediates for the above developed protocol for the synthesis of benzimidazole as follows (scheme-3)

Table 4. [a]Zn and $NaHSO_3$ mediated reduction to amines

Entry	Reactant	Product	Time (min)	Yield (%)[b]	Melting point[c] (^oC)
1			50	93	289-290[37]
2			70	83	>290
3			80	90	200-202[37]
4			50	85	238-240[37]
5			45	89	254-255[37]
6			90	87	290-292[38]
7			60	90	277-279[37]
8			70	94	289
9			45	93	196-198[39]
10			80	90	240-242[38]
11			50	87	>290[40]
12			60	89	267-270[40]

[a]Reaction of nitro compound (1mmol), Zn (3 mmol), $NaHSO_3$ (6 mmol) in water at 100 ^oC for different time intervals on magnetic stirrer. [b]Isolated yields. [c]Melting points of the isolated compounds.



Scheme 3: Proposed mechanism for the synthesis of benzimidazole derivatives

Conclusion

We have developed a novel and efficient protocol through one pot reductive cyclocondensation of 2-nitroaniline with aromatic aldehydes to benzimidazole with $Zn/NaHSO_3$ in water. The fascinating part of our method in comparison to the conventional methods is its simplicity, cost effectiveness, environmentally benign approach and a less time consuming process. We also earn that $Zn/NaHSO_3$ in water is also a better chemoselective reducing system to reduce nitro to amine. Thus, it could potentially be complementary to follow the existing methods for the synthesis of biologically active benzimidazoles moiety.

Acknowledgment

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