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# An Efficient and Green Synthesis of Benzimidazole Derivatives Using SBA-15 Supported Cobalt Nanocatalysts

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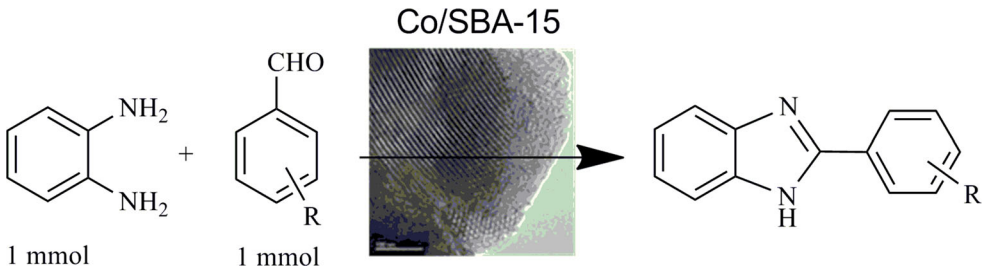
**Abstract** Benzimidazole derivatives have attracted a significant attention in recent years because of their medicinal applications as antiviral, antiulcer, antifungal, antihypertensive, anticancer, and antihistamine compounds. The one-pot synthesis of benzimidazole derivatives via oxidative condensation of aromatic aldehydes with *o*-phenylenediamines under mild conditions was successfully accomplished using a cobalt(II) supported on mesoporous silica-type material. The supported cobalt catalyst could be easily recovered after reaction completion and reused seven times with an excellent durability and without any noticeable loss in activity.

*Graphical Abstract*




**Keywords** Benzimidazoles · Heterogeneous catalysis · Supported cobalt nanocatalyst

## 1 Introduction

Benzimidazole derivatives have attracted a significant attention in recent years because of their medicinal applications as antiviral [1], antiulcer [2], antifungal [3], antihypertensive [4], anticancer [5], and antihistamine [6] compounds. Apart from therapeutic applications, benzimidazoles also play an important role as intermediates in different organic reactions [7, 8]. Two general methods are reported for the synthesis of 2-substituted benzimidazoles; (1) coupling of phenylenediamines and carboxylic acids [9] or their derivatives (nitriles, imidates, or orthoesters) [10] as well as (2) a two-step procedure that consists of the oxidative cyclodehydrogenation of aniline Schiff's bases, which are

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often generated in situ from the condensation of phenylenediamines with aldehydes [11]. The first method often requires strong acidic conditions, sometimes combined with very high temperatures. The second method offers a broad applicability because of the availability of a large variety of aldehydes and oxidative reagents (i.e. nitrobenzene, 1,4-benzoquinone, air, heteropoly acids, $MnO_2$, $Pb(OAc)_4$, $H_2O_2$/HCl etc.). An alternative protocol for the synthesis of benzimidazoles is the one-pot tandem synthesis from alcohols in the presence of bifunctional catalysts, where alcohols are in situ oxidized to aldehydes followed by cyclo-condensation with amine compounds [12–14]. However, multistep processes, drastic reaction conditions, tedious work-up procedures and low yields are among major drawbacks of these methods. The additional serious drawbacks relate to the use of homogeneous catalysts that are somewhat modified in the work-up procedure and cannot be recovered. In the light of these premises, the design of heterogeneous catalysts for a direct, simple and highly selective benzimidazole synthesis will be highly beneficial.

In recent years, the use of heterogeneous catalysts has received considerable interest in the synthesis of various benzimidazole derivatives. Different oxide based supported or unsupported catalysts including aluminosilicates [15], iron oxide [16], cobalt oxide [17], ZnO [18], CuO [19] and $MoO_3$ [20] have already been explored. Supported heteropolyacid catalysts have also shown very good efficiency in such processes [21–23]. Recently, an efficient room temperature synthesis of benzimidazole has been described using zeolite catalysts under shorter reaction time [24]. Excellent yields of 2-aryl-1-arylmethyl-1*H*-benzimidazoles were also obtained using highly reusable Amberlite IR-120 in aqueous media [25]. Expensive gold catalysts on different support (e.g. $TiO_2$, $Al_2O_3$, ZnO, polyurea and hydrotalcite) have been recently utilised for the synthesis of benzimidazoles from 2-nitroanilines under mild reaction conditions [26]. In the course of reaction, 2-nitroanilines was hydrogenated to *o*-phenylenediamine which subsequently underwent cyclization in presence of $CO_2$ and $H_2$. An interesting organic–inorganic hybrid porous iron–phosphonate material containing both micropores and mesopores and a high Fe loading (26.7 wt%) has also been explored by Dutta et al., which showed excellent catalytic activity for the synthesis of benzimidazole derivatives under mild conditions [27].

Most reported heterogeneously catalysed protocols nevertheless require high catalyst loadings, expensive and/or sophisticated catalysts to be developed, low catalyst stability or high loadings of metals [15–27]. Consequently, the design of low metal loaded catalysts featuring a good stability, activity and environmentally friendly nature can provide additional advantages to existing methodologies in the synthesis of benzimidazole derivatives.

In continuation of our work on the development of low loaded, environmentally sound, affordable, stable and selective heterogeneous catalysts for greener organic reactions, herein we report the use of a previously reported reusable effective catalytic system based on cobalt (II) on a mesoporous silica support (Co/SBA-15) for the synthesis of benzimidazole compounds under mild reaction conditions. The proposed catalytic system possesses inherent advantages for benzimidazole synthesis including high activity and stability, low metal loading in the catalyst as well as the use of a relatively inexpensive transition metal (Co) system and an unprecedented low catalyst loading in the reaction (0.004 mmol Co, 0.014 mg catalyst).

## 2 Experimental

### 2.1 Preparation of SBA-15 Supported Cobalt Nanocatalyst (Co/SBA-15)

Salicylaldehyde (2 mmol, 0.244 g) was added to an excess of absolute MeOH, to which 3-aminopropyl (trimethoxy) silane (2 mmol, 0.352 g) was subsequently added. The solution instantly became yellow due to imine formation. After 3 h, cobalt (II) acetate, $Co(OAc)_2{\cdot}2H_2O$ (1 mmol, 0.248 g) was added to the solution and the mixture further stirred for 3 h to allow the new ligands to complex the cobalt. A colour change from pink to olive green is observed. Mesoporous silica (average pore diameter 60 Å, 3 g) was activated by refluxing in concentrated hydrochloric acid (6 M) and then washed thoroughly with the deionized water and dried before undergoing chemical surface modification. This activation treatment readily hydrolyses the siloxane Si–O–Si bonds to Si–OH species which will be key to anchor the cobalt complex. The complex and the activated silica were then mixed and the mixture stirred overnight. The solvent is removed using a rotary evaporator, and the resulting olive green solid dried at 80 °C overnight. The final product was washed with MeOH and water (to remove all physisorbed metal species) until the washings were colourless. Further drying of the solid product was carried out in an oven at 80 °C for 8 h.

### 2.2 General Procedure for the Synthesis of Benzimidazoles

In a typical run, a 50 mL round bottom flask with a magnetic stir bar was charged with aldehyde (1 mmol), *o*-phenylenediamine (1 mmol), Co/SBA-15 nanocatalyst (0.004 mmol, 0. 014 g) and ethanol (2 mL) under oxygen atmosphere at 60 °C for 4 h. The progress of reaction was monitored by TLC (EtOAc: Hexane = 1:5). After reaction completion, the solvent was removed under vacuum and

ethyl acetate (5 mL) was poured to the residue. Then, the reaction mixture was filtered off and the Co/SBA-15 nanocatalyst was rinsed twice with EtOAc (10 mL) and reused; the filtrate was dried over sodium sulfate and the solvent was removed under vacuum, the obtained solid was purified by recrystallization in ethanol in a similar way to that previously reported [28].

## 3 Results and Discussion

Full characterization details of Co/SBA-15 have been previously reported [28]. Typically, cobalt loading was around 0.3 mmol $g^{-1}$ and surface and textural properties of Co/SBA-15 provided a surface area of 450 $m^2$ $g^{-1}$, with a pore size of 3.6 nm and 0.77 $cm^3$ $g^{-1}$ mesoporous pore volume, with an excellent homogeneous dispersion of cobalt oxide species on the SBA-15 support. At the preliminary stage of this work, the reaction of *o*-phenylenediamine and benzaldehyde (1:1 mol ratio) was studied at various catalysts loading to evaluate the catalytic efficiency of Co/SBA-15. A range of solvents including ethanol, methanol, acetonitrile, dichloromethane and dioxane were employed at different temperatures and times to optimize the reaction conditions. Under catalyst free condition, only trace amounts of benzimidazole could be detected at room temperature. Even after refluxing the two reactants in ethanol without catalyst, trace amount of products were observed. The role of catalyst was consequently important for the proposed reaction as even quantities as small as 1 mol% catalyst at room temperature could afford 55 % benzimidazole yield after 6 h of reaction. A significant increase in yields (98 %, Table 1, entry 4) was observed when the reaction was carried out under ethanol reflux. Screening of other solvents (Table 1, entries 5–7) did not provide any significant improvements in yields so that ethanol was then selected as optimum solvent for the reaction.

The effect of catalyst loading was subsequently addressed, with catalyst amounts varied from 1 to 0.4 mol%. Reaction yields were shown to be very consistent (98 %, Table 1, entry 11) even at catalyst loadings up to 0.4 mol%. However, yields dropped to 80 % and below with a further decrease in catalyst loading (0.3 mol % and below). Temperatures employed under optimized reaction conditions (typically 60 −70 °C) did not seem to have a significant effect in reaction yields which were only slightly reduced (>90 %). Optimization studies provided optimum reaction conditions for 4 h reaction at 60 °C using 0.4 mol% catalyst (Table 1, entry 13). Such conditions were consequently selected for further experiments in this work (Scheme 1).

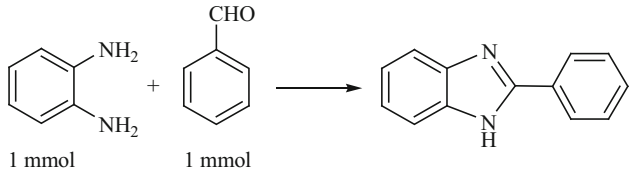
**Table 1** Screening of reaction conditions in the synthesis of benzimidazole from benzaldehyde and *o*-phenylenediamine

| Entry | Catalyst (mol%) | Solvent | *T* (°C) | *t* (h) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | – | – | RT | 6 | Trace |
| 2 | – | EtOH | 78 | 6 | Trace |
| 3 | 1 | – | RT | 6 | 55 |
| 4 | 1 | EtOH | 78 | 6 | 98 |
| 5 | 1 | MeCN | 81 | 6 | 90 |
| 6 | 1 | $CH_2Cl_2$ | 40 | 6 | 72 |
| 7 | 1 | Dioxane | 100 | 6 | 95 |
| 8 | 1 | MeOH | 65 | 6 | 94 |
| 9 | 0.8 | EtOH | 78 | 6 | 98 |
| 10 | 0.5 | EtOH | 78 | 6 | 98 |
| 11 | 0.4 | EtOH | 78 | 6 | 98 |
| 12 | 0.3 | EtOH | 78 | 6 | 94 |
| 13 | 0.4 | EtOH | 60 | 4 | 98 |
| 14 | 0.4 | EtOH | 60 | 2 | 90 |

Reaction conditions: 1 mmol *o*-phenylenediamine, 1 mmol benzaldehyde, 2 mL solvent

*RT* room temperature

[a] Isolated yield

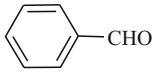
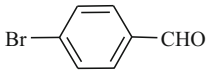
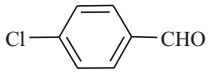
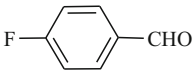
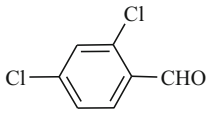
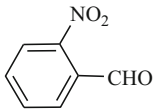
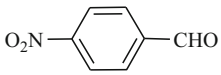
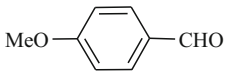
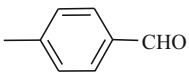
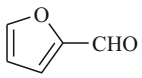
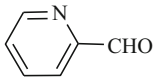



**Scheme 1** Synthesis of benzimidazole from *o*-phenylenediamine and benzaldehyde using Co/SBA-15 as catalyst. Reaction conditions: 1 mmol *o*-phenylenediamine, 1 mmol benzaldehyde, 2 mL solvent, 25–100 °C

The scope and efficiency of the proposed protocol was subsequently investigated for a series of substituted benzaldehydes with electron donating and electron withdrawing substituents with *o*-phenylenediamine under optimum reaction conditions (Table 2; Scheme 2). In addition to benzaldehydes, furan and pyridine-based aldehydes were also tested. In all cases, good to excellent yields (85–96 %) were achieved. Aldehydes with electron withdrawing groups provided relatively higher yields as compared to aldehydes bearing electron donating groups, a very common behavior in coupling-type reactions.

The reason of the high activity of the catalyst could be due to the plausible coordination of cobalt sites (Lewis acidic) [28, 29] to the carbonyl oxygen atom of the aromatic aldehyde, thereby activating the carbonyl group. From Table 2, it is clear that the one-pot condensation reaction is almost equally tolerant (shows almost negligible

**Table 2** Synthesis of various 2-arylbenzimidazoles catalyzed by supported cobalt based on SBA-15

| Entry | Aldehyde | Yield (%)[a] |
|---|---|---|
| 1 |  | 98 |
| 2 |  | 92 |
| 3 |  | 94 |
| 4 |  | 91 |
| 5 |  | 96 |
| 6 |  | 90 |
| 7 |  | 95 |
| 8 |  | 86 |
| 9 |  | 88 |
| 10 |  | 85 |
| 11 |  | 90 |

[a] Isolated yield

yield difference, ca. 10 %) for both electron donating and electron withdrawing substituents on the aromatic ring. These results may suggest a sufficiently strong catalyst/carbonyl oxygen interaction to subsidize the effect of the substituents, irrespective of the nature of the substituents on the benzaldehyde substrate.

Reuse reactions were then carried out under similarly optimized conditions to demonstrate the stability of the catalyst. Co/SBA-15 exhibited excellent recoverability and reusability properties over seven successive runs under identical reaction conditions to those of the first run (Fig. 1). A slight deactivation could be only observed after seven reaction runs. Further ICP/MS analysis of the reaction mixture indicate negligible quantities of Co leached into solution (<5 ppm) which also pointed out the stability and potential of the Co-based catalyst for the proposed benzimidazole synthesis.

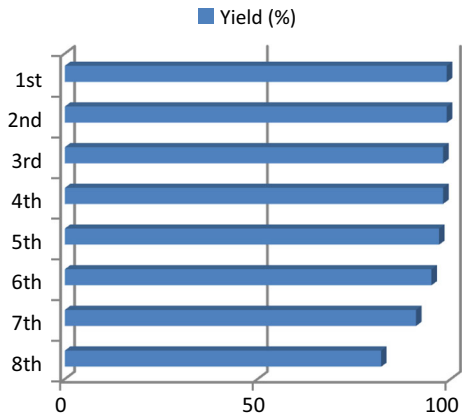
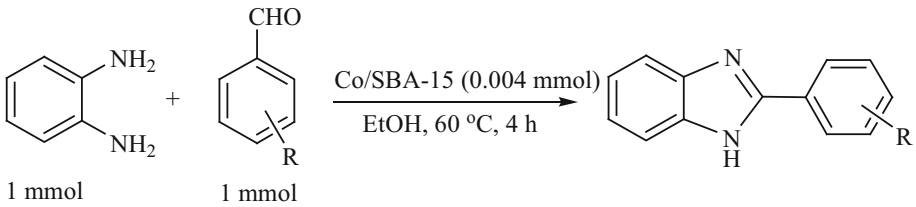



**Fig. 1** Reusability of Co/SBA-15 catalyst in the oxidative condensation of *o*-phenylenediamine and benzaldehyde. Reaction conditions: 5 mmol *o*-phenylenediamine, 5 mmol benzaldehyde, 0.02 mmol Co/SBA-15, 10 mL EtOH, 60 °C, 4 h reaction

**Scheme 2** Synthesis of benzimidazoles from *o*-phenylenediamine and different benzaldehydes using Co/SBA-15 as catalyst at optimal conditions



## 4 Conclusion

A simple, efficient and environmentally friendly approach for the synthesis of substituted benzimidazoles has been developed by a one-pot reaction of *o*-phenylenediamine with aromatic aldehydes in the presence of catalytic amounts of low-loaded Co-containing SBA-15. The supported Co/SBA-15 nanocatalyst could be easily recovered from the reaction mixture and reused seven times without any loss in activity. No metal leaching was observed during the reaction which also demonstrates the potential of the catalyst in greener organic reactions as compared to most reported heterogeneously catalysed protocols to date.

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