

Ag STA: Green and an Efficient Catalyst for Synthesis of Benzimidazole Derivatives at Room Temperature.

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ABSTRACT

A recyclable heterogeneous catalyst was prepared and successfully employed for the simple, convenient, and efficient one-pot synthesis of substituted benzimidazole derivatives from *o*-phenylenediamine and aryl aldehydes. The silver salt of silicotungstic acid was found to be an economical and reusable catalyst, affording the desired products with a low catalyst loading of 10 mol%. The reactions proceeded smoothly to give moderate to high yields (61–86%) within 4.5–10 h. The recyclability of the catalyst, together with its simple operation and efficient catalytic performance, demonstrates the potential of this protocol as a greener approach to the synthesis of substituted benzimidazole derivatives.

Keywords: Ag STA, efficient synthesis, *o*-phenylene diamine, benzimidazole, room temperature.

I. INTRODUCTION

The benzimidazole scaffold has attracted considerable attention in organic and medicinal chemistry because of its broad range of biological and biochemical properties. Benzimidazole is a structural component of vitamin B12 and is closely related to the purine nucleus, which is present in several biologically important molecules. Benzimidazole derivatives constitute an important class of heterocyclic compounds and are found in numerous biologically active molecules exhibiting antiviral, antihypertensive, anticancer, and other pharmacological activities [1,2]. In particular, benzimidazole-containing compounds have demonstrated significant activity against a variety of viral pathogens, including human immunodeficiency virus (HIV) [3,4], herpes simplex virus type 1 (HSV-1) [5], RNA viruses [6], and influenza virus [7]. Among these compounds, 2-substituted benzimidazole derivatives have received particular attention because of their diverse and potent biological activities [8]. Furthermore, benzimidazole derivatives can function as ligands for transition-metal ions in biological systems and have been investigated for their potential therapeutic applications, including the treatment of hypertension and obesity [9,10]. The wide-ranging biological applications of benzimidazole derivatives have therefore stimulated considerable interest in the development of efficient synthetic methods for their preparation.

Several synthetic approaches have been developed for the preparation of benzimidazole derivatives. One of the classical methods involves the cyclocondensation of *o*-phenylenediamine with carboxylic acids or their derivatives. However, this approach generally requires strong acidic conditions and elevated temperatures. Another widely employed strategy involves the oxidative cyclodehydrogenation of Schiff bases, which are generated in situ or isolated from the condensation of *o*-phenylenediamine with aldehydes. This approach has become one of the most commonly used methods for the synthesis of substituted benzimidazoles. Various oxidizing agents and catalysts, including ceric ammonium nitrate (CAN), K₃PO₄, Oxone®, sulfamic acid, DDQ, PhI(OAc)₂, iodine, and KHSO₄, have been reported for this transformation [11–17].

In addition to these reagents, a wide variety of catalytic systems have been explored, including metal halides, metal oxychlorides [18–22], metal oxides, *p*-toluenesulfonic acid (PTSA), metal triflates, air [23–29], ionic liquids, heteropoly acids, BDSB, proline, and various solid- and polymer-supported catalysts. Microwave-assisted and clay-catalyzed approaches have also been investigated. Despite these advances, several reported procedures are associated with limitations such as harsh reaction conditions, prolonged reaction times, moderate yields, tedious work-up procedures, the use of environmentally undesirable reagents or solvents, and the formation of unwanted side products.

Therefore, the development of an efficient, mild, operationally simple, and recyclable catalytic protocol for the synthesis of benzimidazole derivatives remains desirable.

In continuation of our interest in the development of efficient heterogeneous catalytic methodologies [30-33], herein we report a convenient one-pot synthesis of biologically relevant 2-substituted benzimidazole derivatives through the condensation of o-phenylenediamine with aryl aldehydes in the presence of silver silicotungstate (Ag-STA). The developed protocol employs a low catalyst loading and provides the desired benzimidazole derivatives in moderate to high yields under mild reaction conditions. Moreover, the heterogeneous nature and recyclability of Ag-STA offer practical advantages, making the present methodology a potentially useful and greener approach to the synthesis of 2-substituted benzimidazole derivatives.

II. EXPERIMENTAL

A. Materials and Methods

All chemicals and reagents were purchased of analytical grade and used without further purification. Melting points were determined by melting point assembly and correlated with literature data. ^1H NMR spectra were recorded on a Bruker AVANCE 600 (600 MHz) spectrometer using TMS as internal standard and DMSO.

B. General reaction procedure for synthesis of benzimidazole derivatives using Ag STA catalyst:

A mixture of o-phenylenediamine (1 mmol) and benzaldehyde (1 mmol) was placed in a 50 mL round-bottom flask. Ag-STA (10 mol%) was then added to the reaction mixture without the use of any solvent. The reaction mixture was magnetically stirred under an open atmosphere at room temperature until completion of the reaction. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, ethyl acetate was added to the reaction mixture, and the heterogeneous mixture was filtered through Whatman filter paper to recover the catalyst. The recovered catalyst was washed with ethyl acetate two to three times, and the combined filtrates were concentrated under reduced pressure using a rotary evaporator. The resulting crude solid was sufficiently pure by TLC using ethyl acetate/hexane (70:30, v/v) as the eluent. Further purification by a short silica-gel column afforded the corresponding pure 2-substituted benzimidazole product. The purified products were characterized by ^1H and ^{13}C NMR spectroscopy.

C. Spectral Analysis of Selective derivative of Benzimidazole

1) 2-phenyl-1H-benzo[d]imidazole (**Table 2, Entry 1**): Yield 88 %; ^1H NMR (400 MHz, CDCl_3): δ 5.04 (s, H), 7.26 (m, 2H), 7.42 (m, H), 7.53 (m, 2H); 7.62 (m, 2H), 8.18 (m, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ : 115.6, 123.2, 127.6, 129.7, 131.2, 133.9, 142.1, 152.7 ppm.

2) 6-methyl-2-phenyl-1H-benzo[d]imidazole (**Table 2, Entry 2**): Yield 74 %; ^1H NMR (400 MHz, CDCl_3): δ : 2.31 (s, 3H), 5.13 (s, H), 7.14 (d, H), 7.42 (m, H), 7.42 (s, H), 7.52 (m, 2H); 7.56 (d, H), 8.22 (m, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ : 21.6, 116.1, 116.4, 125.9, 127.7, 129.3, 130.9, 131.1, 132.8, 134.6, 135.8, 152.7 ppm.

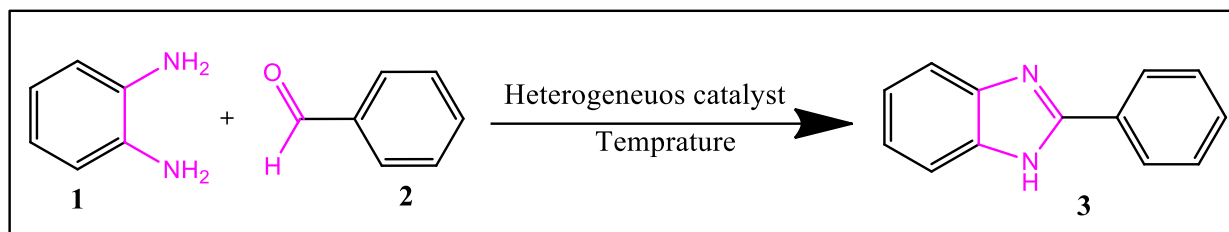
III. RESULTS AND DISCUSSION

To evaluate the catalytic performance of Ag-STA, the model reaction for benzimidazole synthesis was carried out using several reported heterogeneous catalysts under the optimized reaction conditions. The comparative results are summarized in Table 1. In entries 1 and 2, AlCl_3 and FeCl_3 were employed as catalysts under solvent-free conditions. Both reactions proceeded relatively slowly and afforded the corresponding benzimidazole products in 66% and 41% yields, respectively, after 8 h. Moreover, separation of the catalyst from the reaction products was relatively difficult when these metal chlorides were used. To further investigate the role of metal salts, the model reaction was performed using $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (10 mol%) under solvent-free conditions. The reaction afforded 31% yield with 82% conversion after the specified reaction time, indicating limited selectivity toward the desired benzimidazole product (entry 3). Similarly, NiCl_2 and $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ afforded the corresponding benzimidazole in 47% and 51% yields, respectively, despite complete conversion of the starting materials (entries 4 and 5).

The catalytic activities of $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ were also examined under the optimized solvent-free conditions. Both catalysts required a considerably longer reaction time and did not provide efficient conversion to the desired product. $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ afforded 32% yield with 88% conversion, whereas $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ gave 48% yield with 61% conversion after 24 h (entries 6 and 7). Furthermore, $\text{Al}(\text{NO}_3)_3$ was evaluated under identical solvent-free conditions. Even after 18 h, the reaction afforded only 28% yield with 57%

conversion (entry 8). In contrast, the use of Ag-STA under the optimized solvent-free conditions resulted in complete conversion of the starting materials and efficient formation of the desired benzimidazole product (entry 9). These comparative experiments demonstrate the distinct catalytic behavior of Ag-STA under the investigated conditions and support its application as a recyclable heterogeneous catalyst for the synthesis of benzimidazole derivatives.

TABLE I. SYNTHESIS OF BENZIMIDAZOLE USING DIFFERENT HETEROGENEOUS CATALYSTS COMPARISON OF AG STA WITH OTHER HETEROGENEOUS CATALYSTS IN OPTIMIZED REACTION CONDITION



Sr. No	Catalyst	Time (h)	Conversion (%)	Yield (%) ^b
1	AlCl ₃	8	100	66
2	FeCl ₃	6	100	41
3	CuCl ₂ .2H ₂ O	12	82	31
4	NiCl ₂	18	100	47
5	COCl ₂ .6H ₂ O	8	100	51
6	CO(NO ₃) ₂ .6H ₂ O	24	88	38
7	Ni(NO ₃) ₂ .6H ₂ O	24	61	42
8	Al(NO ₃) ₃	18	57	28
9	Ag STA	06	100	89

^a All reactions were carried out on 1.0 mmol of diamine and aldehyde using catalytic amount of catalyst in solvent free condition. ^b Yield refers to the isolated product, characterized by ¹H and ¹³C NMR, and FT-IR.

The model reaction was subsequently investigated in a range of solvents to examine the effect of the reaction medium. However, none of the solvents examined resulted in complete conversion of the starting materials. Based on these screening experiments, the optimized reaction conditions were established as 10 wt% Ag-STA under solvent-free conditions at room temperature.

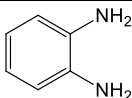
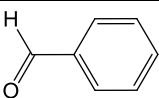
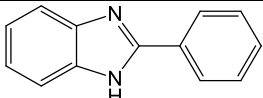
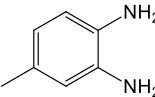
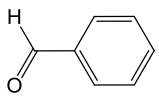
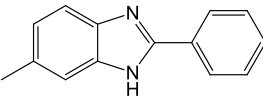
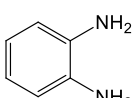
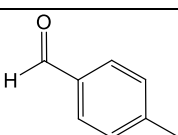
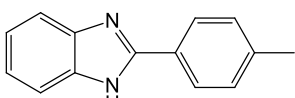
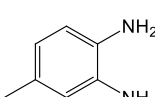
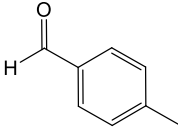
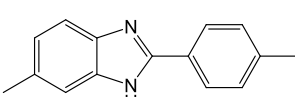
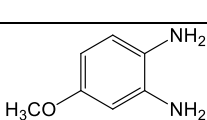
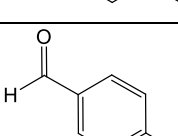
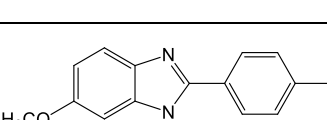
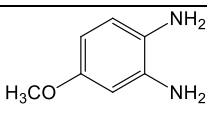
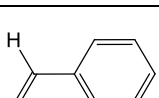
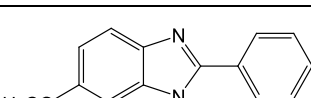
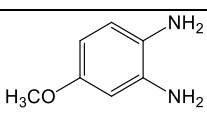
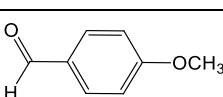
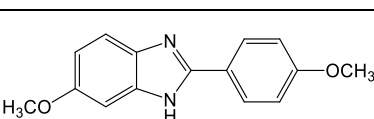
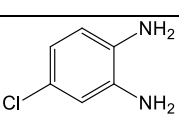
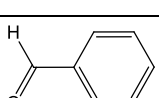
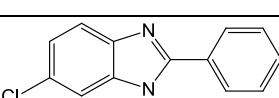
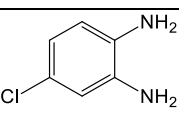
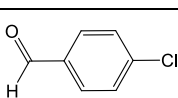
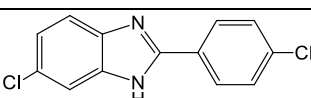
With the optimized conditions in hand, the scope and generality of the developed protocol were investigated by employing a diverse range of commercially available substituted o-phenylenediamines and structurally varied aromatic aldehydes. The reactions were performed under the optimized conditions, and the results are summarized in Table 2. As evident from Table 2, the substituted o-phenylenediamines and aldehydes underwent the cyclocondensation reaction smoothly to afford the corresponding benzimidazole derivatives in moderate to good yields. The reactions generally proceeded within relatively short reaction times using a small amount of catalyst, demonstrating the operational simplicity of the developed protocol.

Initially, unsubstituted benzene-1,2-diamine (o-phenylenediamine) was reacted with benzaldehyde in the presence of 10 wt% Ag-STA under the optimized solvent-free conditions. The reaction afforded the corresponding benzimidazole in 86% yield after 7 h (Table 2, entry 1). Subsequently, a range of o-phenylenediamines and aromatic aldehydes bearing both electron-donating and electron-withdrawing substituents were examined. Most of the investigated substrates underwent cyclization smoothly and afforded the corresponding benzimidazole derivatives in good to efficient yields (entries 5–9). These results indicate that the Ag-STA-catalyzed protocol tolerates a variety of substituents on the aromatic rings. Importantly, the functional groups present in the starting materials remained intact under the optimized reaction conditions, demonstrating the functional-group compatibility of the developed catalytic system.

IV. CONCLUSIONS

In the present study, an efficient one-pot, solvent-free protocol has been developed for the synthesis of substituted benzimidazole derivatives at room temperature using silver silicotungstate (Ag-STA) as a recyclable heterogeneous catalyst. The catalyst was prepared according to a reported literature procedure and successfully applied to the cyclocondensation of *o**-phenylenediamines with aromatic aldehydes. Under the optimized conditions, the use of 10 mol% Ag-STA afforded complete conversion of the starting materials and the corresponding benzimidazole products in yields of up to 86%. The catalyst could be recovered and reused for up to six consecutive cycles without a significant loss in catalytic performance or product selectivity. The developed protocol offers several practical advantages, including simple operation, mild reaction conditions, solvent-free processing, straightforward work-up, and catalyst recyclability. These features make the Ag-STA-catalyzed methodology a useful approach for the synthesis of substituted benzimidazole derivatives.

TABLE II. SYNTHESIS OF DIFFERENT SUBSTITUTED BENZIMIDAZOLE DERIVATIVES USING AG STA IN OPTIMIZED REACTION CONDITION ^a.

Sr. No	Diamine	Aldehyde	Product	Time (h)	Yield ^b (%)
1				6	86
2				5	74
3				6	81
4				6	69
5				10	61
6				6	78
7				4.5	83
8				7	81
9				6	83

^a All reactions were carried out on 1.0 mmol of diamine and aldehyde using catalytic amount of catalyst in solvent free condition. ^b Yield refers to the isolated product, characterized by ¹H and ¹³C NMR, and FT-IR.

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