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5-sulfosalicylic acid as an efficient organocatalyst for environmentally benign synthesis of 2-substituted benzimidazoles

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ABSTRACT

A water soluble, Bronsted acid, 5-sulfosalicylic acid as an efficient organocatalyst was used for the synthesis of physiologically active 2-substituted benzimidazole derivatives from *o*-phenylenediamine and aromatic aldehydes in ethanol at reflux condition. Cost-effectiveness, use of non-hazardous solvents, metal free and commercially available catalyst, single-step, environmentally friendly green method, high conversions, cleaner reaction profiles and simple experimental and workup procedures are the remarkable features of this method.

***Keywords**: 5-SSA, o-Phenylenediamine, Aromatic aldehydes, 2-Substituted benzimidazoles.*

1. Introduction

Benzimidazole is an aromatic N-heterocycle formed by the fusion of benzene and imidazole ring. The most prominent compound available in the nature containing benzimidazole skeleton is *N*-ribosyl-dimethylbenzimidazole, which serves as axial ligands for cobalt in vitamin B_{12} [1]. Benzimidazole and their derivatives are prominent N-heterocyclic compounds which have garnered severe research interest on account of their interesting biological and pharmacological properties [2-7]. In addition, organic compounds possessing the benzimidazole skeleton showed significant activity against several viruses such as human cytomegalovirus (HCMV) [8], Herpes (HSV-1) [9] and influenza [10]. Owing to the unique biological applications of benzimidazole derivatives, a number of approaches have been reported in the literature employing variety of catalysts such as Cp_2ZrCl_2 [11], TiO_2 NPs [12], CuI NPs [13], imidazolium trifluoroacetate protic ionic liquid [14], water mediated [15], bentonite clay [16], Ag_2CO_3/celite [17], UHP/silica phosphoric acid [18], P_2O_5-SiO_2 [19], silica-bonded propyl-*S*-sulfonic acid [20], metal hydrogen sulfates [21], etc. under various reaction conditions.

However, most of these methods are although efficient but still they suffers from certain drawbacks such as expensive reagents, prolonged reaction time, strongly acidic conditions, unsatisfactory yields and tedious workup procedures for the isolation of the pure product. Though the rare earth metal catalyst give better yields, the prohibitive cost of the catalysts make them inappropriate for industrial purpose. Therefore, to avoid these limitations, the introduction of environmentally-benign and economically viable chemical process accompanied with higher yields and superior to the existing methods is in a great demand. It is well understood that organocatalysts are simple organic molecules which are able to promote a wide range of chemical transformations with high beneficial significance over environmental protection. Despite this observation, they also show prominent characteristic properties such as hydrophilic nature, low-cost, metal-free environment, non-toxic, air stable, and eco-friendly nature [22-25]. With these observations in mind, we wish to present a practical and cost-effective protocol, where a simple water-soluble bronsted acid, 5-sulfosalicylic acid (5-SSA) was selected as a sole catalytic component to promote the desired transformation with excellent yield.

2. Experimental

5-sulfosalicylic acid (Spectrochem), *o*-phenylene diamine (Thomas Baker), and aromatic aldehydes (Spectrochem and Thomas Baker) were used as

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received. All the reactions were carried out under open atmosphere in dried glassware. The melting points of all synthesized compound were recorded using hot paraffin bath and are uncorrected. The IR spectra were recorded on Perkin-Elmer Spectrum one FT-IR spectrometer in the frequency range 500-4000 cm^{-1}. The NMR spectra were recorded on a Bruker Avance (300 MHz for ^{1}HNMR and 75 MHz for ^{13}CNMR) spectrometer using $CDCl_3$ as solvent using Tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are expressed in parts per million (ppm) values with the TMS as an internal reference, and coupling constants (*J*) are expressed in hertz (*Hz*). The Mass spectra were recorded on a Shimadzu QP2010 GCMS.

2.1. General procedure for the synthesis of 2-substituted benzimidazole derivatives

To the well stirred mixture of *o*-phenylenediamine (1 mmol), aryl aldehyde (1 mmol) in ethanol (5 mL) was added 5-SSA (20 mol%) and the materials were stirred at reflux condition in preheated oil bath. Upon the completion of reaction confirmed by TLC (n-hexane: ethyl acetate, 3:1), ice cold water was poured into the reaction mixture and stirred continuously at room temperature until free flowing solid was obtained into the reaction flask. The contents were filtered and the product was washed with water, dried and purified by recrystallization from hot ethanol to give the desired product with high purity. The 5-SSA is water soluble which is recovered by removal of solvent from the filtrate under vacuum, dried, and then used for the next cycle.

Selected spectral data

2-Phenyl-1H-benzimidazole (Table 3, entry 1):

m.p.= 293-295°C. ^{1}HNMR (300 MHz, $CDCl_3$): δ= 7.85-7.90 (m, 2H), 7.74-7.79 (m, 5H, Ar-H), 7.41-7.45 (d, 2H, *J*=8.4 *Hz*), 5.45 (s, 1H, NH) ppm. ^{13}CNMR (75 MHz, $CDCl_3$): δ= 111.0, 121.4, 122.0, 126.1, 128.7, 128.9, 129.5, 129.9, 130.4, 130.6, 137.5, 144.2, 155.1 ppm. FT-IR: $\bar{\nu}$ = 3364, 3051, 2942, 1531, 1388, 1275, 967, 825, 744, 655 cm^{-1}. MS (EI): *m/z*= 194 $[M]^{+}$.

2-(4-Nitrophenyl)-1H-benzimidazole (Table 3, entry 2):

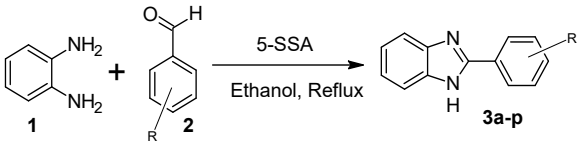
m.p.> 300°C. ^{1}HNMR (300 MHz, $CDCl_3$): δ= 8.34-8.36 (d, 2H, *J* = 7.8 *Hz*, Ar-H), 8.23-8.26 (d, 2H, *J*= 8.4 *Hz*, Ar-H), 7.58-7.61 (m, 2H), 7.19-7.22 (m, 2H), 5.53 (bs, 1H, NH) ppm. ^{13}CNMR (75 MHz, $CDCl_3$): δ 111.5, 114.8, 119.7, 121.4, 125.5, 128.6, 130.5, 136.2, 142.8, 144.7, 149.5, 154.8, 158.4 ppm. FT-IR: $\bar{\nu}$ = 3101, 3060, 1699, 1650, 1630, 1600, 1512, 1340, 1227, 1158, 1106, 1031, 962, 855, 743, 703, 593 cm^{-1}. MS (EI): *m/z*= 239 $[M]^{+}$.

3. Results and discussion

In continuation of our previous research work for development of sustainable methodology for the synthesis of 2-substituted benzimidazoles [11], we report herein 5-SSA for the condensation reaction of *o*-phenylenediamine with diverse aromatic aldehydes in ethanol at reflux condition (Scheme 1).

Initially, a model reaction of *o*-phenylenediamine and 4-nitrobenzaldehyde was refluxed in ethanol in the presence of 5-SSA (20 mol%) to obtain the corresponding 2-(4-Nitrophenyl)-1*H*-benzimidazole. Optimization of the above model reaction was carried out by altering the organic solvent, amount of the incorporated catalyst and the reaction temperature. In this context, the effect of catalytic loading on the course of reaction was examined (Table 1). It was observed that the catalytic loading had a strong influence on the yield of desired product. We analyzed the model reaction by varying the amount of the catalyst from 5 mol% to 30 mol% (Table 1, entry 1-5). The optimum amount of catalyst turned out to be 20 mol% in order to obtain the best result (Table 1, entry 4).

Our initial efforts were focused on investigation of the effect of temperature and solvent on the synthesis of 2-substituted benzimidazoles in the presence of 5-SSA (20 mol%). In a pilot experiment, the model reaction was carried out in ethanol at room temperature, which affords the anticipated product in lower yield (Table 2, entry 1).



Scheme 1. 5-SSA catalyzed synthesis of 2-substituted benzimidazoles.

Table 1. Effect of the amount of 5-SSA on the yield of model reaction.[a]

Entry	Catalyst (mol%)	Time (min)	Yield (%)[b]
1	5	55	58
2	10	55	64
3	15	55	75
4	20	55	92
5	30	55	92

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), 4-nitrobenzaldehyde (1 mmol), and 5-SSA in ethanol at reflux condition.
[b]Isolated yield.

Surprisingly, the model reaction at elevated reaction temperature gives the corresponding product in excellent yield, which was assumed to be the result of a significant role played by the catalyst in this transformation at high temperature. It was found that the best results were obtained in ethanol at reflux condition. At temperature lower than reflux, the yield of the product sharply decreases even with longer reaction times (Table 2, entry 2 and 3). In pursuance of making this protocol environmentally green and economical viable, ethanol was employed as the solvent, which furnishes the desired product in excellent yield at reflux condition (Table 2, entry 4). Unfortunately, unsatisfactory yields were detected for the model reaction in other solvents such as EDC, THF, DMF, methanol and water (Table 2, entry 5-9).

Next, we turned our attention to explore the generality of protocol for synthesis of structurally diverse 2-substituted benzimidazoles by using *o*-phenylene diamine with variety of substituted aromatic aldehydes and the results are shown in Table 3. It was observed that aryl aldehydes possessing electron withdrawing groups afforded excellent yield with shorter reaction times as compared to aldehyde with electron donating groups (Table 3, entries 2-4 and 5-8).

Table 2. Effect of the solvent on the reaction time and yield of the model reaction.[a]

Entry	Reaction condition	Time (min)	Yield (%)[b]
1	Ethanol/RT	120	45
2	Ethanol/50°C	90	74
3	Ethanol/70°C	90	82
4	Ethanol/Reflux	55	92
5	EDC/Reflux	55	53
6	THF/Reflux	55	58
7	DMF/Reflux	55	64
8	Methanol/Reflux	55	68
9	Water/Reflux	55	70

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), 4-nitrobenzaldehyde (1 mmol), and 5-SSA (20 mol%) in solvent (5 mL) at given temperature.
[b]Isolated yields.

Table 3. 5-SSA catalyzed synthesis of 3a-3p.[a]

Entries	Aryl aldehyde	Product	Time (min)	Yield[b] (%)	m.p. (°C)		Ref.
					Found	Reported	
1	Benzaldehyde	3a	65	94	293-295	294-295	[33]
2	4-Nitrobenzaldehyde	3b	55	92	>300	322-323	[33]
3	4-Chlorobenzaldehyde	3c	60	89	300-301	300	[34]
4	4-Cyanobenzaldehyde	3d	56	90	261-263	262	[35]
5	4-Hydroxybenzaldehyde	3e	70	86	274-275	275	[34]
6	4-Methoxybenzaldehyde	3f	75	85	224-225	223-226	[34]
7	3-Methoxybenzaldehyde	3g	68	84	216-218	217-219	[36]
8	4-Methylbenzaldehyde	3h	72	86	121-122	120-122	[36]
9	2,5-Dimethoxybenzaldehyde	3i	78	83	219-220	218-220	[37]
10	3,4,5-Trimethoxybenzaldehyde	3j	95	76	260-261	260	[11]
11	Furfuraldehyde	3k	90	81	285-286	286	[34]
12	Thiophene-2-carbaldehyde	3l	85	85	215-216	214-217	[36]
13	Acetaldehyde	3m	120	70	175-177	174-176	[38]
14	2-Napthaldehyde	3n	90	78	216-217	217	[35]
15	9-Anthraldehyde	3o	95	80	260-261	261-263	[39]
16	Ferrocenecarboxaldehyde	3p	90	82	209-210	208-210	[11]

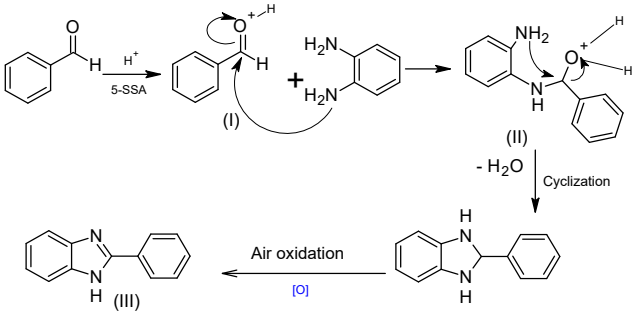
[a]Reaction conditions: *o*-phenylenediamine (1 mmol), aryl aldehyde (1 mmol), and 5-SSA (20 mol%) in ethanol (5 mL) at reflux condition.
[b]Isolated yield.

The sterically crowded aldehydes such as 2,5-dimethoxybenzaldehyde as well as 3,4,5-trimethoxybenzaldehyde (Table 3, entries 9 and 10) were also reacted efficiently affording the desired product in moderate yields. Fascinatingly, hetero-aromatic aldehydes such as furfuraldehyde and thiophene-2-carbaldehyde (Table 3, entries 11 and 12) reacted smoothly with *o*-phenylenediamine giving the estimated products in excellent yields. Interestingly, aliphatic aldehyde such as acetaldehyde reacted slowly with *o*-phenylenediamine giving comparatively moderate yield (Table 3, entries 13). To our delight, the polycyclic aromatic aldehyde such as 2-napthaldehyde and 9-anthraldehyde (Table 3, entries 14 and 15) and organometallic aldehyde such as ferrocenecarboxaldehyde (Table 3, entry 16) were also tolerated efficiently with the substrate molecules affording anticipated product in satisfactory yield.

The mechanistic pathway for the synthesis of 2-substituted benzimidazoles catalyzed by 5-SSA is depicted in Scheme 2. At the beginning, bronsted acid activates the carbonyl carbon of aldehyde to give intermediate **(I),** which rapidly undergoes nucleophilic attack of amino group of *o*-phenylenediamine to form the intermediate **(II),** which on intramolecular cyclization loses the water molecule followed by consequent air oxidation to form the target molecule **(III)**.

Reusability is one of the important aspects of the catalyst from both the economical as well as environmental standpoint. Therefore, we examined the effectiveness of 5-SSA for the model reaction. Upon the completion of reaction, the catalyst was recovered and reused for the next cycle for subsequent reaction. It was found that the catalyst showed a substantial reusability up to the fifth cycle without any notable reduction in the yield of desired product (Table 4).

The comparison of 5-SSA with the other reported catalyst employed for reaction of benzaldehyde with *o*-phenylenediamine is shown in Table 5. The result reveals that 5-SSA is a highly efficient catalyst at reflux condition in terms of reaction time and yield for the synthesis of 2-substituted benzimidazole derivatives.



Scheme 2. Plausible mechanism for synthesis of 2-substituted benzimidazole derivatives.

Table 4. Reusability of 5-SSA for the yield of model reaction.[a]

No. of Cycle	Time (min)	Yield (%)[b]
1	55	92
2	55	90
3	55	90
4	55	88
5	55	86

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), 4-nitrobenzaldehyde (1 mmol), and 5-SSA (20 mol%) in ethanol (5 mL) at reflux condition.
[b]Isolated yield.

Table 5. Comparison with variety of catalysts for the reaction of *o*-phenylenediamine and benzaldehyde.

Sr. No.	Catalyst	Amount of catalyst (mol%)	Temp. (°C)	Time	Yield (%)	Ref.
1	5-SSA	20	Reflux	65 min	94	This Work
2	NH_4OAc	100	75	4.5 h	95	[35]
3	Saccharose	20	45	1 h	80	[36]
4	$[pmim]BF_4$	75	RT	5 h	85	[39]
5	$CoCl_2.6H_2O$	10	RT	4 h	81	[40]
6	$MnFe_2O_4$ NPs	10	RT	4 h	92	[41]
7	UHP/I_2	20	70	30 min	87	[42]

4. Conclusion

In summary, a simple and cost-effective route for the synthesis of 2-substituted benzimidazoles was developed by using *o*-phenylenediamine with diverse aromatic aldehydes in presence of catalytic amount of 5-sulfosalicylic acid in ethanol at reflux condition. The simplicity, efficiency, greener reaction conditions, high yield of products, easy work-up procedure and use of a catalytic amount of 5-SSA make it a green protocol. Another important feature of this methodology is the use of a metal free catalyst and avoidance of hazardous organic solvents.

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