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RESEARCH ARTICLE

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Zinc Sulfamate Catalyzed Efficient Selective Synthesis of Benzimidazole Derivatives Under Ambient Conditions

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Abstract: Zinc sulfamate ($Zn(NH_2SO_3)_2$ is a derivative of sulfamic acid (H_3NSO_3) which possesses "Lewis acidity" and finds well suited in a number of catalytic applications. The present paper describes an efficient, eco-friendly, and clean synthesis of 2-substituted benzimidazole derivatives by reacting diverse o-phenylenediamine with various substituted aromatic aldehydes using a catalytic amount of zinc sulfamate in ethanol at ambient temperature. As a result, 10 mol.% of Zinc sulfamate catalyst showed 92% of respective product yield with 100% conversion using short reaction period in ethanol. Meanwhile, effect of reaction parameters, such as amount of catalyst, different solvents, and reaction temperature on reaction product, was also studied. In addition, in the optimized reaction condition various substituted biological important benzimidazoles derivatives were prepared by using optimized reaction condition in good to efficient yield. In addition, possible reaction mechanism in the presence of zinc sulfamate for the preparation of benzimidazole derivative was sketched and discussed. The present green approach showed significances with faster reaction rate with inexpensive catalyst, which showed excellent and clean yield of benzimidazole in mild reaction condition with easy work-up procedure.

Keywords: Benzimidazole derivatives, zincsulfamate, diamine reaction, green efficient catalysis, ambient reaction conditions, selective derivative preparation.

1. INTRODUCTION

N-heterocyclic compounds are the most abundant and integral scaffolds that occur ubiquitously in a large number of bioactive natural products, drug intermediates, pharmaceuticals, and agrochemicals. Benzimidazoles are a privileged class of compounds among the N-heterocycles with a diverse spectrum of biological activities and therapeutic potentialities including anti-ulcers, anti-hypertensives, antivirals, anti-fungals, anti-cancers, anti-histaminics, and also exhibiting medicinal properties such as serotoninergic 5-HT3 and 5-HT4 receptors in the CNS [1, 2]. In addition, the unique benzimidazole moiety plays a significant role in anti-inflammatory, anti-analgesic, antioxidant, anti-diabetic, selective neuro peptide YY1 receptor antagonists, anti-malarial, anti-tubercular, *etc.*, drugs [3-7]. Moreover, benzimidazoles are very important intermediates in dyes and polymer synthesis having widespread applications in fluorescence, chemosensing, crystal engineering, and corrosion science [8]. Additionally, with their pharmaceutical significance, benzimidazoles form constant complexes with various transition group metals [9]. Some reports are available on the formation of mono, bi and tridentate co-ordination structures associated with 2-substituted imidazole and benzimidazole based structures and the chelation with various ligands [10]. Some of the commercially important benzimidazole product structures, which are industrially very important, are illustrated in Fig. (**1**).

Due to their widespread use in different engineering applications, considerable efforts have been paid to develop efficient methods for the preparation of benzimidazole derivatives [11-14]. Some of the common methods involve condensation of o-phenylenediamine with carbonyl-containing compounds, such as aldehydes, carboxylic acid, and acid halides, in the presence of various catalysts and hazardous solvents [15-17]. Recently, countless catalysts and oxidative reagents have been testified in literature for the synthesis of benzimidazole

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3.3.13. 2- [4-(Trifluoromethyl)phenyl]-1H-benzimidazole (3m)

^{1}H NMR (in δ ppm): 8.50 (d, 1 H), 7.72 (d, 1 H), 7.65-7.58 (m, 2 H), 7.36 (d, 1H), 7.28 (d, 1 H), 5.2 (s, 1H, NH); ^{13}CNMR (δ): = 154.57, 142.3, 137.82, 132.05, 125.94, 125.03, 123.89, 122.87, 114.7; IR (in cm^{-1}): 3440, 2350, 2134, 1656, 1034, 832; Analy. Calcd. for $C_{14}H_9F_3N_2$:C 64.12, H3.46, F 21.73, N 10.68; Observed: C 64.16, H 3.44, F 21.75, N 10.65; MS (m/z): 262.

3.3.14. 2-(2-Hydroxyphenyl)-1H-benzimidazole (3n)

^{1}H NMR (in δ ppm): 7.72-7.65 (m, 3H), 7.30-7.25 (m, 3 H), 7.05 (d, 2 H), 5.2 (s, 1H, NH); ^{13}C NMR (in δppm): 160.28, 158.60, 145.77, 135.81, 133.52, 128.05, 125.58, 120.57, 116.84, 115.69; IR (in cm^{-1}): 3585, 3470, 2198, 1659, 1607, 1096, 927, 756. Analy. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33; O, 7.61; Observed: C, 74.28; H, 4.80; N, 13.31; O, 7.61; MS (m/z): 211.

CONCLUSION

In conclusion, we have developed a simple and efficient method for the synthesis of benzimidazole derivatives using zinc sulfamate [$Zn(NH_2SO_3)_2$] as a catalyst under mild reaction conditions with competitive and high yield. The advantages of the present techniques are operational simplicity, high efficiency, no side products formation, easy workup procedure, and less reaction time. Additional reaction parameters, such as catalyst amount, effect of temperature, and various organic solvents, were tested to obtain optimized reaction condition to give the satisfactory yield of benzimidazole. A number of different structurally diverse benzimidazole derivatives were prepared in optimized reaction condition using zinc sulfamate as a catalyst. All different synthesized benzimidazole moieties in this report are important pharmacophores in several pharmaceutically important compounds and useful intermediate for the synthesis of a wide variety of bioactive natural products. Furthermore, a detailed and probable sketched mechanism fits very well for the formation of benzimidazole derivatives with zinc sulfamate catalyst, providing secondary support to the proposed hypothesis and obtained results. Thus, we believe that, the present protocol is an efficient and simplest alternative path to synthesize benzimidazole derivative on both small and large-scale preparations.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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spectra were recorded on a Perkin-Elmer spectrophotometer using KBr pellets. ^{1}HMR spectra were recorded on Varian Gemini (200 MHz) spectrometer using DMSO-d_6 as solvent and TMS as internal standard. ^{13}C-NMR spectra were recorded on 50 MHz in DMSO-d_6 solvent, in δ ppm. All chemical shifts values are reported in δ scale downfield from TMS.

3.3. Spectral Study of Synthesized Products 3 (a-n)

3.3.1. 2-Phenyl-1H-benzimidazole (3a)

^{1}H-NMR spectrum (200MHz, DMSO-d6, in δ ppm): 8.15 (m, 3H), 7.92 (t,1H), 7.5-7.4 (m, 4H), 7.3 (t, 1H), 5.2 (s, 1H, NH); ^{13}C-NMR (50 MHz, DMSO-d6, in δ ppm): 114.7, 118.9, 121.4, 123.4, 126.4, 129.0, 129.8, 130.1, 136.4, 145.5, 153.0. FT-IR (KBr) in cm^{-1}: 3048, 2260, 1665, 1418, 1280; Analy. Calcd. for $C_{13}H_{10}N_2$: C 80.39, H 5.19, N 14.42; Observed: C 80.42 H 5.18 N 14.40; MS (m/z): 194

3.3.2. 2-(4-Methoxyphenyl)-1H-benzimidazole (3b)

^{1}H NMR (in δ ppm): 8.19 (dd, 2H), 7.66 (d, 1 H), 7.45 (d, 1 H), 7.24-7.10 (m, 2H), 7.13 (d, 2H), 5.2 (s, 1H, NH), 3.86 (s, 3H); ^{13}C NMR (in δ ppm): 158.38, 152.86, 139.88, 129.22, 124.67, 124.19, 122.20, 120.46, 114.30, 113.16, 58.31; IR (in cm^{-1}): 3450, 2242, 2120, 1655, 1045; Analy. Calcd. for $C_{14}H_{12}N_2O$: C 74.98, H 5.39, N 12.49, O 7.13; Observed: C 75.02, H 5.37, N 12.50, O 7.11; MS (m/z): 224.

3.3.3. 4-(1H-benzo[d]imidazol-2-yl)-N, N-dimethylaniline (3c)

^{1}H NMR (in δ ppm): 8.20 (dd, 2 H), 8.15-8.05 (m, 2 H), 7.24–7.10 (m, 2 H), 7.13 (d, 2 H), 5.2 (s, 1H, NH), 3.21 (s, 6 H); ^{13}C NMR (in δ ppm): 152.65, 152.06, 141.72, 130.09, 126.51, 124.82, 123.09, 120.66, 115.41, 112.93, 42.51; IR (in cm^{-1}): 3507, 2876, 2193, 2170, 1658, 1620, 1026, 970,749; Analy. Calcd. for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71; Observed: C, 75.89; H, 6.38; N, 17.73; MS (m/z): 237

3.3.4. 2- [4- (2-propyl) phenyl]- 1H-benzimidazole (3d)

^{1}H NMR (in δ ppm): 8.15 (d, 2 H), 7.72 (d, 1 H), 7.58 (d,1H) 7.36 (d, 2 H), 7.22-7.15 (m, 2H), 5.2 (s, 1H, NH), 2.95 (m, 1 H), 1.26 (d, 6H); ^{13}C NMR (in δ ppm): 151.33, 149.40, 143.85, 136.16, 128.77, 126.94, 126.43, 122.23, 120.65, 116.56, 112.20, 40.20, 24.00; IR (in cm $^{-1}$): 3456, 2350, 2127, 1665, 1073; Analy. Calcd. for $C_{16}H_{16}N_2$: C 81.32, H 6.82, N 11.85; Observed: C 81.32, H 6.80, N 11.87; MS (m/z): 236.

3.3.5. 2-(4- Methylphenyl)-1H- benzimidazole (3e)

^{1}H NMR (in δ ppm): 8.09 (dd, 2 H), 7.65-7.52 (m, 2 H), 7.22–7.09 (m, 2 H), 6.87 (d, 2 H), 5.2 (s, 1H, NH), 2.71 (s, 3 H); ^{13}C NMR (in δ ppm): 154.17, 144.68, 138.55, 130.92, 126.00, 123.94, 123.02, 120.87, 116.07, 115.06, 23.83; IR (in cm^{-1}): 3460, 2880, 2254, 1655, 1605, 980, 853, 762; Analy. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45; Observed: C, 80.75; H, 5.82; N, 13.43; MS (m/z): 208

3.3.6. 2-(2- Nitrophenyl)-1H- benzimidazole (3f)

^{1}H NMR (in δ ppm): 8.09-8.21 (m, 3 H), 7.58-7.43 (m, 1 H), 7.38-7.24 (m, 2 H), 6.91 (d, 2 H), 5.2 (s, 1H, NH); ^{13}C NMR (in δ ppm): 153.09, 152.16, 142.75, 138.55, 135.41, 130.31, 127.20, 124.14, 122.89, 116.81; IR (in cm^{-1}): 3503, 1660, 1603, 1425, 1284, 960, 865, 745; Analy. Calcd. for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56; O, 13.38; Observed: C, 65.30; H, 3.78; N, 17.55; O, 13.37; MS (m/z): 240 (M + 1).

3.3.7. 2-(3-Nitrophenyl)-1H- benzimidazole (3g)

^{1}H-NMR (in δ ppm): 8.86(s, 1H), 8.46 (d,1H), 8.24 (d, 1H), 7.89 (m, 1H), 7.53 (m, 2H), 7.24(m, 2H), 5.2 (s, 1H, NH); ^{13}C-NMR (in δppm): 150.6, 144.82, 136.05, 132.20, 129.02, 128.95, 126.88, 123.74, 122.89, 119.02, 112.23. IR (KBr in cm^{-1}): 3060, 1524, 1450, 1357, 973, 746; Analy. Calcd. for $C_{13}H_9N_3O_2$: C 65.27, H 3.79, N 17.56, O 13.38; Observed: C 65.32, H 3.77, N 17.55, O 13.36; MS (m/z): 239.

3.3.8. 2-(4-Nitrophenyl)-1H- benzimidazole (3h)

^{1}H-NMR (in δ ppm): 8.32 (d, 2H), 7.6-7.4 (m, 2H), 7.3-7.1 (m, 4H), 5.2 (s, 1H, NH); ^{13}C-NMR (in δppm): 155.17, 148.70, 142.85, 137.74, 127.90, 125.25, 123.97, 117.81. IR (KBr in cm^{-1}): 3385, 1675, 1602, 1524, 1457, 1286, 966, 887, 750; Analy. Calcd. for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56; O, 13.38; Observed: C, 65.25; H, 3.80; N, 17.58; O, 13.37; MS (m/z): 239.

3.3.9. 2-(4-Chlorophenyl)-1H-benzimidazole (3i)

^{1}H-NMR (in δ ppm): 8.25(d, 2H), 7.6 (d, 2H), 7.45 (m, 2H), 7.20 (m, 2H), 5.2 (s, 1H, NH); ^{13}C-NMR (in δ ppm): 152.6, 145.9, 134.3, 130.4, 129.7 128.9, 128.2, 124.1, 116.4; IR (KBr in cm^{-1}): 3045, 1670, 1603, 1460, 1400, 1285, 965, 750; Analy. Calcd. for $C_{13}H_9ClN_2$: C 68.28, H 3.97, Cl 15.50, N 12.25; Observed: C 68.25, H 3.96, Cl 15.55, N 12.24; MS (m/z): 228.

3.3.10. 2-(2-Chlorophenyl)-1H-benzimidazole (3j)

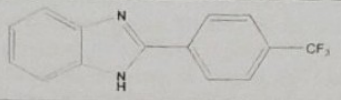
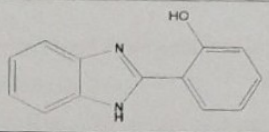
^{1}H-NMR (in δ ppm): 8.31 (d, 1H), 7.62 (t, 2H), 7.41 (d, 2H), 7.3-7.1 (m, 3H), 5.2 (s, 1H, NH); ^{13}C-NMR (in δ ppm): 154.2, 143.7, 140.0, 134.4, 131.7, 130.3 129.2, 127.3, 124.6, 117.9; IR (KBr in cm^{-1}): 3105, 1674, 1608, 1466, 1440, 1275, 960, 766; Analy. Calcd. for $C_{13}H_9C_lN_2$: C 68.28, H 3.97, Cl 15.50, N 12.25; Observed: C 68.27, H 3.95, Cl 15.55, N 12.23; MS (m/z): 228.

3.3.11. 2-(4-Bromophenyl)-1H-benzimidazole (3k)

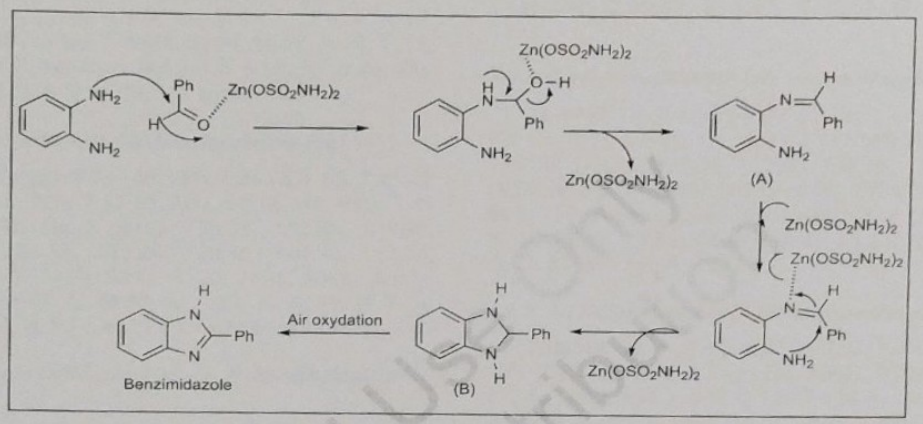
^{1}H NMR (in δ ppm): 8.20 (d, 2H), 7.66 (d, 2 H), 7.66-7.48 (m, 2 H), 7.23-7.12 (m, 2H), 5.2 (s, 1H, NH); ^{13}C NMR (inδ ppm): 155.14, 142.06, 133.85, 131.74, 130.47, 124.56, 123.37, 115.22; IR (in cm^{-1}): 3325, 2167, 2119, 1650, 1035, 827; Analy. Calcd. for $C_{13}H_9$ Br N_2: C 57.17, H 3.32, Br 29.26, N 10.26; Observed: C 57.20, H 3.32, Br 29.24, N 10.25; MS (m/z): 272.

3.3.12. 2-(4-Fluorophenyl)-1H-benzimidazole (3l)

^{1}H NMR (in δ ppm): 8.26 (d, 2H), 7.55-7.46 (m, 2 H), 7.35 (dd, 2 H), 7.26-7.15 (m, 2 H), 5.2 (s, 1H, NH); ^{13}C NMR (in δppm): 165.62, 155.16, 145.86, 134.68, 130.14, 125.74, 124.26, 120.17, 114, 110.88; IR (in cm^{-1}): 3450, 2268, 2120, 1659, 1026, 833. Analy. Calcd. for $C_{13}H_9FN_2$: C 73.57, H 4.27, F 8.95, N13.20; Observed: C 73.55, H 4.30, F 8.98, N 13.17; MS (m/z): 212.

Entry	Product	Time (h)	M.P. (°C)	Yield (%) [b]
13		2.20	265	88
14		3.20	240	85

Reaction conditions: diamine (0.01 mol), aldehyde (0.01mol), catalyst (10 mol. wt) Reaction time is monitored by TLC. **(b)** Isolated yield.



Scheme (1). Probable mechanism for $Zn(NH_2SO_3)_2$ catalysedsynthesis of 2-substituted benzimidazoles.

we have carried out one more trial of the reaction of benzaldehyde with orthophenylene diamine in the presence of nitrogen environment under same reaction conditions prescribed in the manuscript. Surprisingly a minute amount of respected product was obtained after refluxing reaction vessels at 80°C temperature in ethanol for 68 hrs. This result showed that inert atmosphere is not promising for current transformation. Moreover, it can be concluded that the intermediate (B) was easily oxidized by oxygen and offered 2-substituted benzimidazoles in short reaction time. The obtained result gives a strong provision to our sketched mechanism.

3. EXPERIMENTAL SECTION

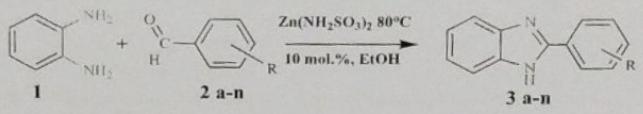
3.1. General

All reagents and intermediates were obtained from commercial suppliers and used without any further purification. Zinc oxide (99.0 %), sulphamic acid (99.0 %), acetonitrile (HPLC grade), ethyl acetate (98.0 %), anhydrous sodium sulfate (98.0 %), and all substrate for ester derivatives were purchased from Sigma-Aldrich and used without any further purification. All solvents were obtained from commercial sources and were distilled with appropriate reagents prior to use. In the present approach, catalyst zinc sulfamate ($Zn(SO_3NH_2)_2$ was prepared by using stoichiometry (2:1) amount of sulfamic acid (NH_3SO_3) and zinc oxide (ZnO). The obtained final zinc sulfamate ($Zn(SO_3NH_2)_2$ powder was directly used as a catalyst for the preparation of benzimidazole derivative. Benzimidazole derivatives were characterized by using TLC, different spectroscopic methods such as ^{1}H NMR, ^{13}C NMR, FT-IR and elemental analysis. In addition, obtained results were compared with reported literature values.

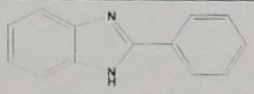
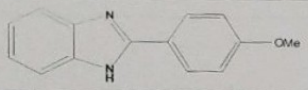
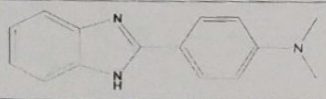
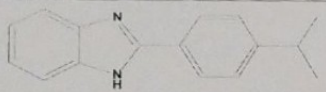
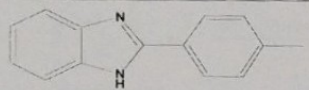
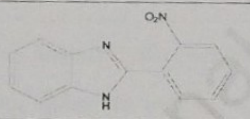
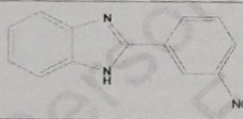
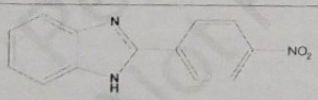
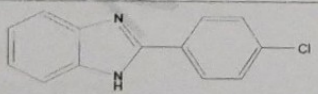
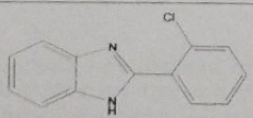
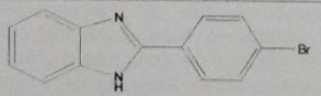
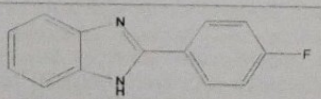
3.2. General Procedure for the Synthesis of Benzimidazole Derivatives

In a 50 ml round bottom flask, mixture of o-phenylenediamine (0.01 mol), aromatic aldehydes (0.01 mol) and ethanol (10 ml) was taken. To this solution, a known amount of catalyst $Zn(NH_2SO_3)_2$ (10 % mole) was added carefully. The resulting reaction mixture was then heated at 80°C reaction temperature with constant vigorous stirring using magnetic stirrer. The reaction progress was monitored by thin layer chromatography (TLC). After completion of the reaction indicated by TLC (TLC solvent system; CH_2Cl_2 and MeOH (90:10)), the reaction mixture was cooled at room temperature and then poured into ice water. The reaction gave a white solid precipitate in the ice-cold water. The precipitated solid was filtered out, washed with ice water three times and further purified by recrystallization with hot ethanol. In addition, purification of the product was carried out by passing sample through a short column of silica gel whenever it is necessary. The obtained pure products were then examined and confirmed by further characterization using ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. All the melting points of prepared compounds were determined in open capillary tubes and are uncorrected. The FT-IR

Table 3. Synthesis of benzimidazole compounds 3(a-n) from diamine and aldehydes under optimized conditions[a].

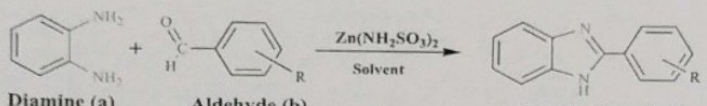


1 2 a-n 3 a-n

Entry	Product	Time (h)	M.P. (°C)	Yield (%)[b]
1		2.00	290	92
2		2.10	234	94
3		1.40	238	90
4		1.50	243	93
5		1.50	224	92
6		2.40	256	84
7		2.30	146	88
8		2.10	314	90
9		1.40	293	88
10		2.50	235	78
11		2.10	260	90
12		1.50	245	90

(Table 3) Contd....

Table 2. Influence of reaction parameters on the benzimidazole yield[a].



Diamine (a) Aldehyde (b) Benzimidazole (c)

Entry	Amount of $Zn(NH_2SO_3)_2$	Solvent	Reaction Temp. (°C)	Reaction Time (h)	Yield (%)[b]
1	5 mol.%	EtOH	80	5.0	56
2	10 mol.%	EtOH	80	2.0	92
3	15 mol.%	EtOH	80	3.0	67
4	10 mol.%	EtOH	60	5.0	62
5	10 mol.%	EtOH	70	5.0	68
6	10 mol.%	EtOH	90	2.0	72
7	10 mol.%	EtOH	100	2.0	65
8	10 mol.%	MeOH	80	3.0	78
9	10% mole	DMF	80	6.0	60
10	10 mol.%	H_2O	80	12.0	42
11	10 mol.%	THF	80	12.0	21
12	10 mol.%	Toluene	80	10.0	40
13	10 mol.%	-	80	8.0	38

Reaction conditions: **(a)** o-Phenylenediamine (0.01 mol), benzaldehyde (0.01mol). Reaction time ismonitored by TLC. **(b)** Isolated yield.

In this regard 1, 2-diamine was reacted with unsubstituted benzaldehyde in the presence of 10 mol.% of a catalyst which showed 92% selective yield of respective benzimidazole in 2 h reaction time (Entry 1). Later on, reactions were performed using electron donating organic group associated 4-methoxy benzaldehyde, which gave us 94% competent yield in 2.10 h (Entry 2). Similarly, the same reaction was also preceded very well with electron-rich substituent as $N(CH_3)_2$, $CH(CH_3)_2$, and CH_3 which also resulted in respective efficient 90%, 93% and 92% yield of benzimidazole (Entry 3-5). In the next step, nitro-substituted functionality at ortho, meta and para on the benzaldehydes showed 84%, 88% and 90% yield of respective benzimidazole using 10 mol.% $Zn(NH_2SO_3)_2$ as a catalyst (Entries 6-8). In addition, aldehydes with chloro substituent also showed efficient performance and obtained quantitative yield (Entries 9 and 10). Whereas, Br, F and CF_3 moieties containing aldehydes also gave moderated yields of benzimidazole respectively (90%, 90% and 88%) (Entries 11-13). Under the given reaction condition, 1,2-diamine reacted with salicyaldehyde showed poor yield and obtained 76% yield of benzimidazole derivative in 3.20 h (Entry 14). However, from these results, it can be concluded that zinc sulfamate is a highly suitable catalyst for the synthesis of benzimidazole with different functional substituents on the aldehyde rings. In addition, these substituted functionalities were preserved throughout the course of reaction in the presence of the prepared catalyst in optimized reaction condition. Additionally, result revealed that aromatic aldehydes with different substituents at meta or para positions showed comparable results towards the formation of benzimidazole derivative. On the other hand, aromatic aldehydes with ortho substitution afforded the desired product in lower to moderate yields (Entries 6, 10 & 14). We believed that in these reactions, the steric hindrance caused a major impact on the yield of respective benzimidazole product formation. In the case of salicyaldehyde along with steric effect, inductive effect directed reaction output. Additionally, intramolecular hydrogen bonding is more effective and stronger in salicyaldehyde than 2-nitrobenzaldehyde which causes the lowering of yield of ortho-hydroxy benzaldehyde reaction. All these synthesized benzimidazole moieties have confirmed the basis of comparing our obtained results and spectral data with physical and spectral data (FT-IR, H1NMR and C13NMR) available in the literature.

2.3. Probable Benzimidazole Formation Mechanism

In order to understand in depth reaction mechanism with zinc sulfamate catalyst for the development of benzimidazole derivatives, the possible reaction mechanism is depicted in Scheme (**1**). A possible mechanism for this one-pot reaction is sketched based on reported literature [44] and obtained results in this study. It is proposed that at the initial stage, a lone pair of electrons on the oxygen atom of aldehyde interacts with zinc sulfamate, which leads to the activation of carbonyl carbon to generate the carbonium ion, resulting in a facile nucleophilic attack of diamine yielding imino compound (A). Furthermore, zinc sulfamate again forms bonding with the nitrogen of the imino group, which activates it and undergoes ring closure by intra molecular attack of the second amino group to obtain (B) followed by air oxidation to offer the desired 2-substituted benzimidazoles. This promising mechanism confirmed that the role of zinc sulfamate is to activate the aldehyde and facilitate facial cyclization, leading to rapid and high yield of benzimidazole. Additionally,

obtain good to efficient yield of respective c and ended with 47% yield in 12 h reaction time (Table **1**, Entry 9).

Meanwhile, we have also tested some solid supported catalyst because supported materials have much attention in organic synthesis and transformation owing to their characteristic properties such as enhance reactivity, easy separation and selectivity. Taking into account $ZnCl_2$ (10 mol. %) supported on fumed SiO_2 catalyst were prepared and tested for the catalytic application. This prepared solid supported Lewis acid catalyst also failed to give the desired product in efficient yield. As a result, this catalyst showed 63% yield of benzimidazole product in 12 h reaction time (Table **1**, Entry 10). We have also compared our results with sulfamic acid because sulfamic acid (Bronsted acid) is one of the excellent acid catalysts in many organic transformations. The catalytic reaction with sulfamic acid for the benzimidazole formation showed good conversion (82 %) of reactant but did not show outstanding selectivity for the formation of benzimidazole. This catalyst showed 56% selective benzimidazole yield with other byproducts at 80°C in 12h reaction time in ethanol (Table **1**, Entry 11) [20-22]. Whereas, the reaction in the presence of zinc sulfamate gave 100% conversion with the selective product in 92% yield in 2h. Thus, zinc sulfamate is of the most effective and selective catalyst for the formation of 2-substituted benzimidazole derivatives in mild reaction condition. Therefore, for further study in this report, we have used and described the results based on $Zn(NH_2SO_3)_2$ catalyzed reactions.

2.2. Influence of Reaction Parameters on the Synthesis of Benzimidazole

As mentioned earlier in this report, lower amount of $Zn(NH_2SO_3)_2$ (5 mol.%) catalyst needs longer reaction time, whereas 10 mol.% catalyst showed outstanding results for the formation of benzimidazole product (Table **2** entry 1 and 2). Furthermore, in order to study in detail the effect of the amount of catalyst in achieving higher yield of benzimidazole, we performed the experiments by using a higher amount of $Zn(NH_2SO_3)_2$ catalyst in ethanol under similar reaction condition. 15 mol. % of $Zn(NH_2SO_3)_2$ catalyst showed 100% conversion of both reactants a and b but obtained 67 % yield of benzimidazole c at 80°C reaction temperature (Table **2**, Entry 3). This reveals that a higher amount of $Zn(NH_2SO_3)_2$ catalyst (more than 10 mole%) showed an adverse effect on the selectivity of benzimidazole and produced some side products [20-22]. The experimental results revealed that 10 mol. % loading of catalyst efficiently utilized 100% reactants and afforded the desired product yield (92%) in short reaction time. Therefore, for further study, 10 mol% of $Zn(NH_2SO_3)_2$ catalyst with 80 °C reaction temperature and 2 h time in ethanol is the optimized reaction condition for this protocol.

Furthermore, to study the effect of temperature on the efficiency of catalytic activity, we have conducted various reactions with 10 mol. % of $Zn(NH_2SO_3)_2$ catalyst in the reaction temperature range from 60-100 °C in ethanol. Entries 4 and 5 in Table **2** show the yield for lower temperature 60 °C and 70 °C, respectively. At these temperatures, reaction showed 62 and 68% yield of benzimidazole correspondingly in 5 h reaction time. However, the reactions performed at 90 and 100°C resulted in lower yield compared with reaction at 80°C temperature. These reactions at 90 and 100 °C resulted in 72% & 65% yield of product, respectively (Table **2** Entries 6 & 7). These results at high temperature indicate that high temperature condition produced some byproducts and lowered the yield of benzimidazole and proved harmful condition for the selective formation of product [20-22]. On the other side, the reaction at 80 °C resulted in outstanding yield of benzimidazole using 10 mol. % catalysts in ethanol. Based on these temperature-screening activities, it is indicated that, 80°C reaction temperature is the most favorable condition for this protocol to produce selective benzimidazole. Therefore, for further study, we have considered 80°C reaction temperature as the optimized condition in this study.

In order to study and understand, the effect of different solvents on the synthesis of selective benzimidazole derivative using $Zn(NH_2SO_3)_2$ catalyst, we have performed various reactions in different solvents using optimized reaction condition and the results are summarized in Table **2** (Entries 8-12). Initially, the synthesis of C was carried out in methanol as solvent using 10 mol % $Zn(NH_2SO_3)_2$ catalyst at 80°C temperature. This reaction showed 78% yield of selective formation of benzimidazole in 3 h reaction time (Entry 8). Entries 9 & 10 show the synthesis of benzimidazole in dimethylformamide (DMF) and water (H_2O) respectively. These reactions revealed an efficient conversion of reactants but provided only 60% and 42% of the desired benzimidazole product, correspondingly in 6 h and 12 h reaction period. Solvents such as tetrahydrofuran (THF) and toluene were found to be inactive for this protocol. These reactions were very sluggish and completed after 12 h & 10 h reaction time. 21% & 40% of selective benzimidazole unsatisfactory yields were obtained in these solvent systems (Entries 11 & 12). However, in the absence of any solvent using 10 mol. % $Zn(NH_2SO_3)_2$ catalyst showed highly efficient conversion but the output of the reaction was 38% yield of product in 8 h and at 80 °C temperature (Entry 13). Drastic decrease in the yield of the product under solvent-free condition was due to the improper solubility of reactant in the reaction system without solvent and eventually the catalytic activity was reduced. These results clearly indicate that the presence of ethanol solvent displays the highly effective catalytic activity, which is a key advantage of this protocol in the synthesis of benzimidazole derivatives.

Based on these screening results experiment, the most advantageous reaction condition was identified as one equiv. of diamine and aldehyde with 10 mol. % of $Zn(NH_2SO_3)_2$ in ethanol at 80 °C reaction temperature. With this optimized reaction condition, we have proceeded to investigate the scope and generality of this protocol using a collection of various substituted aromatic aldehydes and diamine in ethanol as a solvent. Consequently, a diversity of commercially accessible different structurally substituted aldehydes was treated in the optimized reaction conditions to obtain benzimidazole derivatives and obtained results are summarized in Table **3**. As shown in Table **3**, all substituted aldehydes participated well in this cyclization reaction and afforded the desired products of benzimidazole in good to efficient yields using the catalytic amount of $Zn(NH_2SO_3)_2$.

the easy separation of products from the reaction mixture, which shows unique efficient and facile, low-cost green protocol for the preparation of benzimidazole derivative.

2. RESULTS AND DISCUSSION

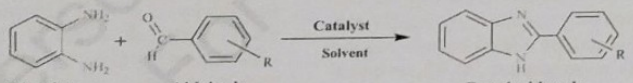
2.1. Influence of Catalyst on the Synthesis of Benzimidazole

Initially, we began with catalyst-free reaction by stirring reaction mixture of a and b in ethanol at room temperature. Additionally, several reactions were performed using various catalysts under different reaction conditions and outcomes of these reactions are given in Table **1**. The catalyst-free reaction failed to produce selective benzimidazole and conversion of reactants in long reaction time and obtained only 21 % conversion with 13 % selective yield of c after 48 h reaction time (Table **1**, Entry 1). Later on, the same reaction was performed at 80°C reaction temperature in ethanol without any catalyst. This reaction obtained 21% improved yield in 24h reaction time with a number of known side products (Table **1**, Entry 2). Moreover, the same catalyst-free reaction was also carried out in DMF to see the effect of solvent on catalyst-free reaction to develop selective product formation. However, this reaction obtained 28 % yield of respective product c in 24h reaction time (Table **1**, Entries 3). All these catalyst-free reactions gave unsatisfactory results and indicated that use of a catalyst is essential for effective and selective yield of benzimidazole.

Later on, to determine the effect of $Zn(NH_2SO_3)_2$ catalyst on the benzimidazole synthesis, we carried out the reaction at the same reaction conditions using 5 mol.% of the catalyst. Tremendously, this reaction showed outstanding results in just 5 h reaction time. As a result, this reaction obtained 56 % selective benzimidazole yield in 5 h reaction time. Furthermore, the same reaction with increased catalyst amount 10 mol. % showed 92 % selective yield of c in similar reaction condition. These reaction results reveal that $Zn(NH_2SO_3)_2$ catalyst has outstanding catalytic property for the synthesis of selective benzimidazole in short reaction period at 80°C in ethanol (Table **1**, Entries 4 and 5). Meanwhile, to compare our catalytic reaction results with some other Lewis and Bronsted acidic catalysts, we performed a number of other reactions using 10 mol. % of different catalysts in the same reaction condition.

Primarily, we performed the reaction of same molar quantity of a and b at 80°C with a catalytic amount of L-Proline in ethanol, this reaction consumed 8 h reaction time with 52 % selective yield of benzimidazole formation (Table **1**, Entry 6). This reaction with L-Proline not only showed poor yield but also obtained some known side products with the benzimidazole [20-22]. However, under similar reaction condition, we have also used poly phosphoric acid (PPA) and $Sc(OTf)_3$ as catalyst for the benzimidazole formation in ethanol. These reaction results obtained, 61% and 28% selective yield of benzimidazole in 12 h reaction time (Table **1**, Entries 7 and 8). Furthermore, the reactions in the presence of PPA and $Sc(OTf)_3$ have certain drawbacks such as long reaction time, in-efficient yield and highly expensive catalysts and lengthy product separation process. Additionally, we have also tested $ZnSO_4$ as a catalyst for the same reaction under the same reaction condition. This catalyst also failed to

Table 1. Effect of various catalysts and solvents on the reaction of *o*-phenylenediamine with benzaldehyde[a].



Diamine (a) Aldehyde (b) Benzimidazole (c)

Sr. No.	Catalyst	Solvent	Reaction Temp. (°C)	Reaction Time (h)	Yield (%) [b]
1	Catalyst free	Ethanol	RT	48	13
2	Catalyst free	Ethanol	80	24	21
3	Catalyst free	DMF	80	24	28
4	$Zn(NH_2SO_3)_2$ (5 mol.%)	Ethanol	80	5	56
5	$Zn(NH_2SO_3)_2$ (10 mol.%)	Ethanol	80	2	92
6	L-Proline	Ethanol	80	8	52
7	PPA	Ethanol	80	12	61
8	$Sc(OTf)_3$	Ethanol	80	12	28
9	$ZnSO_4$	Ethanol	80	12	47
10	$ZnCl_2$-SiO_2	Ethanol	80	12	63
11	Sulfamic acid	Ethanol	80	12	56

[a]**Reaction conditions:** o-Phenylenediamine (0.01 mol), benzaldehyde (0.01mol). [b]Isolated yield.

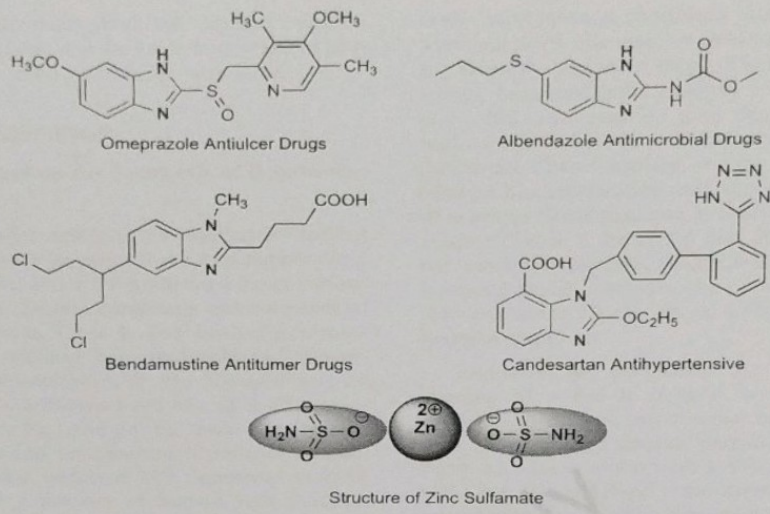


Fig. (1). Examples of important commercial drugs containing benzimidazole structural moiety as well as the structure of zinc sulfamate catalyst.

derivatives from the cyclo-condentation of 1,2-arylenediamines with aldehydes. Some of these reagents are summarized here, sulphur, $Sc(OTf)_3$ or $Yb(OTf)_3$[18], H_2O_2-HCl [19], Silica-Sulphuric acid [20-22], NH_4Br [23], nitrobenzene (high boiling oxidant/solvent) [24], Lewis acids like pyridinium-p-toluene sulfonate, ionic liquids [25] like polyaniline-sulfate and zeolite. Furthermore, $FeCl_3$-doped polyaniline nano-particles [26], and some of the solid acids have been also reported for the preparation of benzimidazole in solvent-free condition [27]. Catalysts such as $SiO_2/ZnCl_2$ [28], cobalt(II) chloride hexahydrate [29], $[Sm(OTf)_3]$ [30], $[In(OTf)_3]$ [31], sodium metabisulfite [32], silphox $[POCl_3\_n(SiO_2)_n]$ [33], potassium persulfate-$CuSO_4$ [34], indion 190 resin [35], ammonium acetate [36], thiamine hydrochloride [37], SDS micelles, DBSA, $Fe_3O_4@SiO_2@(NH_4)_6$–Mo_7O_{24} magnetic core-shell nanocomposite, Boron tri-fluoride etherate ($BF_3.OEt_2$), Cu-nano particles/SiO_2, LiBr, and GO-HSO_4 [38-41], were utilized in the same procedure. On the other hand, a number of available protocols have not been entirely satisfactory because of some disadvantages like unpleasant yields of product, side product formation, elongated reaction period, and lengthy and harsh workup techniques. Additionally, hazardous acidic environments, the necessity of additional amounts of co-catalyst, cumbersome experimental processes and use of moisture-sensitive and costly catalysts have some negative impacts on the reported methods. Therefore, the development of simple, efficient, high yield green synthetic approach for the synthesis of biologically active compounds is one of the major challenges in organic synthesis. To overcome all these disadvantages, a practical, inexpensive and green method for the synthesis of benzimidazole derivatives with a readily available catalyst is required in the scientific community.

Sulfamates are the derivatives of sulfamic acid. It is a well known concept that sulfamic acid readily forms various derivatives of metal sulfamates with the metal or with respective carbonates, oxides, or hydroxides. Zinc sulfamate is one of the efficient, non-toxic, inexpensive and readily available sulfamic acid derivatives and can act as a "Lewis acid" catalyst in a number of organic transformations. Zinc sulfamate is commercially available but still it has not been much explored. Recently, the catalytic activity of zinc sulfamate was found prominent for the synthesis of dihydropyrimidone derivative [42]. Zinc triflate very much resembles with zinc sulfamates. Ramineni Srinivasulu and coworkers evaluated the catalytic activity of zinc triflate for the synthesis of benzimidazole and described excellent results [43]. Based on these results and in view of the efforts toward the development of a simple, mild, eco-friendly reaction protocol, we explored the potential of zinc sulfamate as a catalyst for the synthesis of benzimidazoles. We have found that zinc sulfamate can smoothly catalyze the selective cyclo-condensation reaction efficiently with the advantages of rapid reaction rates, high yields, no corrosion of equipment, ease of manipulation, and low-cost catalyst. These characteristics prompted us to extend the scope of zinc sulfamate catalyzed cyclization for the synthesis of benzimidazole derivatives.

Herein, we present the efficient, simple, and economical cheap method for the preparation of benzimidazole derivatives catalyzed by readily available zinc sulfamate catalyst. The present reaction protocol was found to be highly selective, efficient, and gave high yield of respective product in short reaction period. To optimize the reaction condition, we have also studied the influence of reaction parameters such as the concentration of catalyst, the effect of solvent, and the effect of temperature on benzimidazole yield and selectivity. At the optimized reaction condition, various substituted benzimidazole derivatives were prepared by using o-phenylenediamine and various substituted aldehydes in the presence of zinc sulfamate in ethanol. We found that the present protocol has easy and simple workup procedure with