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Contributed Paper

Gallocyanine as An Efficient Catalyst for Synthesis of Benzimidazoles in Aqueous Ethanol

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ABSTRACT

The benzimidazole derivatives have been obtained catalyzed by gallocyanine. A wide range of aromatic aldehydes easily undergo condensation with substituted o-phenylendiamine under mild conditions to afford the target molecules in excellent yields. The products were obtained in 80–93% yields in 30–80 min. The method has several advantages such as use of green solvent, easy work-up, excellent yield and avoiding use of inconvenient preparation of catalyst. Meanwhile, the catalyst gallocyanine is a kind of inexpensive catalyst, which might be applied to broad green catalytic system.

Keywords: benzimidazole, gallocyanine, aromatic aldehyde, heterocycles

1. INTRODUCTION

In recent years, benzimidazoles are notable for their application in medicinal chemistry, benzimidazole ring is an important pharmacophore in modern drug discovery, are found in various biologically active and have applications as diverse therapeutic agents, including antihypertensives, antifungals, anticancers, and antihistaminics[1-3]. Because of their importance, the synthesis of substituted benzimidazoles has become a focus of synthetic organic chemistry. Numerous synthetic strategies for the synthesis of benzimidazoles have been demonstrated by employing aromatic aldehydes and *o*-phenylenediamines promoted by catalysts such as acidic ionic liquid [4], $Ce(NO_3)_3 \cdot 6H_2O$ [5], ZnO-NPs [6], Ag_2CO_3/Celite [7], KI [8], CMK-5-SO_3H [9], $Ru(bpy)_3Cl_2$/O_2 [10], Co/Ce-ZrO_2 [11], CdSe nanocomposites [12]. Meanwhile, gallocyanine is one kind of dye additive agent, which has a high conjugation system and containing acidic and alkaline groups, easily soluble in polar solvents. On the other hand, these previous reported multicomponent reactions, in spite of the merits of these procedures, each of them suffers more or less from one of the following limitations: low yields, unavailability of the reagents, long reaction times, inconvenient preparation of catalyst, expensive base, effluent pollution, harsh reaction conditions, and even tedious work-up procedures, may limit the functional group compatibility and their application. New methodologies from commercial substrates and environmentally reaction system, with high efficiency, under mild conditions, are still a research field of undoubted current

attention. As part of our program aimed at developing new synthetic useful methodologies with cheap catalyst and environmental friendly reaction system, in continuation of our work to develop novel catalyzed system to synthesize such kinds of compounds, we employ inexpensive and green gallocyanine as catalyst to obtain 2-arylbenzimidazoles in this research.

2. EXPERIMENTAL

2.1 Apparatus and Analysis

Melting points were measured on an Electrothemal X6 microscopy digital melting point apparatus. IR spectra were recorded on a Bruker Equinox 55 spectrometer using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker AVANCE 400 (400 MHz) instrument with the TMS at d 0.00 ppm as an internal standard. C, H and N analysis were performed by a Perkin-Elmer 2400 CHN elemental analyzer. Chemicals used were of commercial grade without further purification.

2.2 General Procedure for the Sysnthesis of Benzimidazole

An equimloar (1 mmol) mixture of an *o*-phenylenediamine **1**, aromatic aldehyde **2**, and gallocyanine (10 mol%) was vigorously stirred at 60°C in EtOH (3 mL) for the specific time indicated by TLC (petroleum ether: ethyl acetate = 4:1) in Table 2. After completion of the reaction, the mixture was quenched by adding H_2O (20 mL), extracted with EtOAc (3 x 10 mL), and the combined extracts were dried by anhydrous $MgSO_4$. The filtrate was evaporated and the corresponding benzimidazole was obtained as the only product. The products **3a–3t** were obtained in 70–95% yields. The structures of the products **3** were identified by their IR, ^{1}H NMR, ^{13}C NMR and elemental analysis spectra. The spectral data of selected products are given below:

*2-(4-Chlorophenyl)-benzimidazole (**3a**)*

white solid; m.p. 295-297 °C; IR (KBr): 3479 (NH),1609 (C=N), cm^{-1}; ^{1}H-NMR (400MHz, DMSO-d_6): δ 13.03 (s, 1H), 8.23 (d, J = 8.5 Hz, 2H), 7.70-7.63 (m, 3H), 7.55 (d, J = 7.2 Hz, 1H), 7.26-7.23 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.8, 143.5, 134.5, 134.3, 129.0, 128.7, 128.1, 122.6, 121.8, 118.7, 111.3; Anal. Calcd. for $C_{13}H_8ClN_3O_2$: C 68.28, H 3.97, N 12.25. Found: C 68.19, H 4.10, N 12.29.

*2-(4-Chlorophenyl)-5-nitrobenzimidazole (**3f**)*

yellow solid; mp 296-298 °C; IR (KBr): 3481 (NH), 1611 (C=N), cm^{-1}. ^{1}H-NMR (400MHz, DMSO-d_6): δ 13.68 (s, 1H), 8.83 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.53 (d, J = 9.0 Hz, 2H), 7.45 (d, J = 9.0 Hz, 2H); ^{13}C NMR: (100 MHz, DMSO-d_6) δ 158.2, 151.1, 135.7, 135.2, 133.3, 131.6, 129.9, 125.0, 124.2, 113.2, 112.6; Anal. Calcd. for $C_{13}H_8ClN_3O_2$: C 57.05, H 2.95, N 15.35. Found: C 57.13, H 2.78, N 15.35.

*2-(4-Methoxyphenyl)-benzimidazole (**3k**)*

white solid; mp 262-264 °C; IR (KBr): 3482 (NH),1608 (C=N), cm^{-1}; ^{1}H-NMR (400MHz, DMSO-d_6): ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.73 (s, 1H), 8.07 (d, J = 8.7 Hz, 2H), 7.54 (m, 2H), 7.18-7.16 (m, 2H), 7.12 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.1, 151.2, 143.4, 134.7, 127.6, 122.1, 121.8, 121.2, 118.1, 114.0, 110.8, 55.1; Anal. Calcd. for $C_{14}H_{12}N_2$: C 74.98, H 5.39, N 12.49. Found: C 74.62, H 5.18, N 12.49.

*2-(4-Nitrophenyl)-benzimidazole (**3r**)*

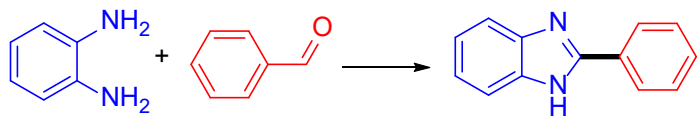
Yellow solid; mp 310-312 °C; IR (KBr): 3485 (NH),1613 (C=N), cm^{-1}; ^{1}H-NMR (400MHz, DMSO-d_6): δ 13.09 (s, 1H), 8.06 (m, 2H), 7.92 (t, J = 8.6 Hz, 1H), 7.80 (*t*, J = 8.8 Hz, 1H), 7.65 (s, 2H), 7.26 (d, J = 4.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.2, 147.2,

143.9, 134.5, 132.8, 130.7, 124.1, 123.3, 121.8, 119.4, 111.8; Anal. Calcd. for $C_{13}H_9N_3O_2$: C 65.27, H 3.79, N 17.56. Found: C 65.36, H 3.68, N 17.49.

3. RESULTS AND DISCUSSION

We firstly examined the activity of reaction system under the condition of *o*-phenylendiamine (1 mmol), 4-cholrobenzaldehyde (1 mmol) and gallocyanine (10 mol%) with different ratio of EtOH and H_2O (3 mL) at 80 °C in 240 min, the results are summarized in Table 1. When the ethanol was employed as solvent in the reaction, the yield of obtained product **3a** was improved to 75% (Table 1, entry 1). And then, the changes of ratio of ethanol and water result the fluctuations in yield, the 60:40 of ethanol and water is best reaction solvent. Next, we optimized the reaction temperature and observed that the yield was improved to 90% at 60 °C (Table 1, entry 8). On the other hand, the amount of catalyst is considerable according to satisfy environmental protect, when we employ the different loading of gallocyanine, the yield of benzimidazole product was changed respectively. After screening all the different reaction condition, we finally observed that the yield of **3a** was improved to highly 92% at 60 °C in 60% aqueous ethanol (3 mL) in the presence of 5 mol% gallocyanine (Table 1, entry 14-16). When we enlarged the scale of this reaction, the good iolated yield 89% of **3a** was obtained as expected (Table 1, entry 17).

Table 1. Optimization of the reaction conditions for the synthesis of compound benzimidazoles. [a]



1 **2** **3a**

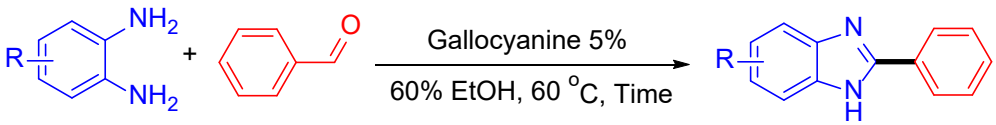
Entry	Catalyst (mol %)	EtOH : H_2O	Temperature (°C)	Time (min)(min)	Yield (%) [b] (%)
1	10	100 : 0	80	60	75
2	10	80 : 20	80	60	80
3	10	60 : 40	80	60	88
4	10	40 : 60	80	60	83
5	10	20 : 80	80	60	78
6	10	0 : 100	80	60	Trace [c]
7	10	60 : 40	70	60	87
8	10	60 : 40	60	60	90
9	10	60 : 40	50	60	86
10	10	60 : 40	40	60	68
11	10	60 : 40	r.t.	60	35
12	0	60 : 40	50	60	Trace [c]
13	2	60 : 40	50	60	86
14	5	60 : 40	50	60	91
15	15	60 : 40	50	60	83
16	20	60 : 40	50	60	85
17 [d]	5	60 : 40	50	60	89

[a] Reaction conditions: *o*-phenylendiamine (1 mmol), 4-cholrobenzaldehyde (1 mmol) and catalyst (gallocyanine 0-20 mol%) in 5 mL solvent [b] Isolated [c] Unknown compounds yield [d] 10 mmol gram-scale reaction under the standard conditions.

Encouraged by these results, we continue to employ the different substituted *o*-phenylendiamines and different substituted aromatic aldehydes to certify application's universality of this procedure under the optimized condition (Table 2).

In all the cases tested, the reaction went smoothly and giving a good yield of the desired product, respectively. As shown in table 2, a variety of *o*-phenylendiamine, bearing not only electron-donating but electron-withdrawing substituents, afforded the products in excellent yields (Table 2, entries 1-6). A series of aromatic aldehyde substrates with electron-rich

Table 2. Synthesis of 2-arylbenzimidazoles using gallocyanine as catalysis.[a]

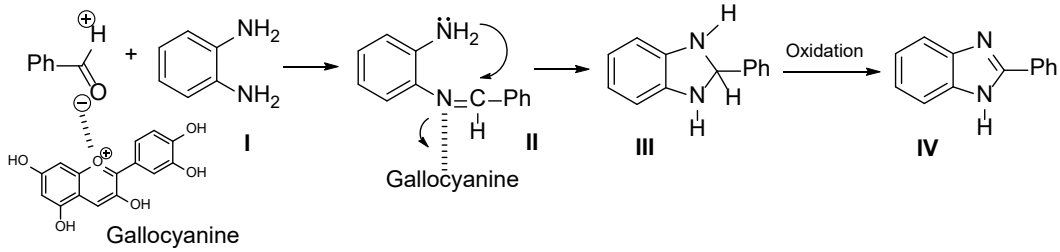


1 **2** **3a**

R = H, Me, OCH_3, Cl, F, NO_2

Entry	R-	Ar-	Compound	Time(min)	Yield [b] (%)	Mp (°C, Lit.)
1	H	4-Cl-C_6H_4	**3a**	40	92	295-297 [14]
2	4-Me	C_6H_5	**3b**	40	85	234-236 [18]
3	4-Br	4-CH_3-C_6H_4	**3c**	30	83	235-237 [20]
4	4-F	4-CH_3-C_6H_4	**3d**	30	92	233-235 [19]
5	4-Cl	4-CH_3-C_6H_4	**3e**	35	85	235-237 [19]
6	4-NO_2	4-Cl-C_6H_4	**3f**	30	90	296-298 [18]
7	H	C_6H_5	**3g**	35	80	286-288 [13]
8	H	2-OH-C_6H_4	**3h**	80	89	181-183 [15]
9	H	4-$N(CH_3)_2$-C_6H_4	**3i**	60	85	285-287 [15]
10	H	3-CH_3O-C_6H_4	**3j**	80	82	210-212 [16]
11	H	4-MeO-C_6H_4	**3k**	50	89	224-226 [17]
12	H	4-Me-C_6H_4	**3l**	40	90	262-264 [18]
13	H	4-Cl-C_6H_4	**3m**	40	87	295-297 [14]
14	H	2-Cl-C_6H_4	**3n**	70	85	227-228 [15]
15	H	3-Br-C_6H_3	**3o**	80	90	249-251 [16]
16	H	4-F-C_6H_4	**3p**	40	82	250-252 [16]
17	H	3-NO_2-C_6H_4	**3q**	35	91	185-187 [15]
18	H	4-NO_2-C_6H_4	**3r**	35	93	310-312 [15]
19	H	2-Furyl-C_6H_4	**3s**	80	82	283-285 [14]

[a] Reaction conditions: *o*-phenylendiamine (1 mmol), aromatic aldehyde (1 mmol) and catalyst (gallocyanine, 10 mol%) in 5 mL EtOH at 60 °C [b] Isolated yield.



Scheme 1. Proposed mechanism for synthesis of benzimidazole.

substituents in the *para, meta* or *ortho* position participation in reaction to give the corresponding products in quite similar high yields (Table 2, entries 13-18) and reaction time in contrast to the case with electron-poor in the *para, meta or ortho* position without formation of any by-products (Table 2, entries 8-12). It is worth mentioning that *ortho* position substitued aldehydes need the longer reaction time because of potential steric effect (Table 2, entries 8, 10, 14, 15). The proposed mechanism for synthesis of benzimidazole using gallocyanine as catalyst is demonstrated. Initially, benzaldehyde is likely to be activated by gallocycanine and reacts with o-phenylendiamine to generate Schiff base (**II)**. Next, intramolecular attack by another amino group on C=N double bond facilitates the formation of hydrobenzimidazole (**II**), which undergoes subsequent air oxidation to give the expected benzimidazole (**Scheme 1**).

4. Conclusions

In conclusion, a facile synthesis of benzimidazoles comprising the reaction of various aldehydes with substituted *o*-phenylendiamine in good to excellent yield is provided using gallocyanine as an efficient catalyst. The protocol overcomes the earlier disadvantages like harsh reaction conditions, tedious work-up, expensive process, waste generation and the use of metallic oxide.

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