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Original Article

Microwave-Assisted, Ionic Liquid-Catalyzed Synthesis of 1,2-Disubstituted Benzimidazoles under Solvent-Free Conditions

Dau Xuan Duc*, Le Duc Giang

Vinh University of Science, 182 Le Duan, Vinh, Nghe An, Vietnam

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Abstract: An efficient method for the synthesis of 1,2-disubstituted benzimidazoles has been developed from 1,2-diaminobenzenes and aldehydes using 1-butyl-3-methylimidazolium ([Bmim]BF_4) as a catalyst under solvent-free conditions. Various products were obtained in good to excellent yields under microwave irradiation. The synthesis features advantages such as short reaction time, environmentally benign conditions, simple work-up procedure, and high efficiency.

Keywords: 1,2-disubstituted benzimidazoles, microwave irradiation, 1,2-diaminobenzenes, cyclization.

1. Introduction

Benzimidazole derivatives constitute an important group of aromatic heterocyclic compounds. Benzimidazoles possess a wide range of biological activities, such as antiarrhythmic, antihistaminic, antiulcer, anticancer, inotropic, antifungal, antihelmintic, and antiviral activities [1-7]. Many benzimidazole-based compounds are famous drugs in the market used to treat various diseases. Candesartan is an antihypertensive agent, whereas astemizole is an effective antihistaminic drug. Bendamustine is a chemotherapy medication used to treat chronic lymphocytic leukemia, multiple myeloma, and non-Hodgkin's lymphoma. Thiabendazole is a preservative, an antifungal agent, and an antiparasitic agent. Omeprazole is a medication used to treat gastroesophageal reflux disease, peptic ulcer disease, and Zollinger-Ellison syndrome. Telmisartan is a drug used to treat high blood pressure, heart failure, and diabetic kidney disease (Figure 1). In addition, the use of benzimidazoles in other fields, such as dyes, chemical sensors, fluorescence, and corrosion science, has also been documented [7-11].

With such a broad range of applications, the synthesis of benzimidazole derivatives has attracted intensive research by chemists with numerous reports in the literature. The cyclization of 1,2-diaminobenzene derivatives with aldehydes is one of the most common and straightforward for preparing these

* Corresponding author.
E-mail address: xuanduc80@gmail.com

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heterocycles. This protocol usually has disadvantages, such as drastic reaction conditions, the use of toxic organic solvents, and long reaction times. The use of microwaves can significantly decrease reaction times, and many methods involving microwave irradiation for this cyclization reaction have been reported recently [12, 13].

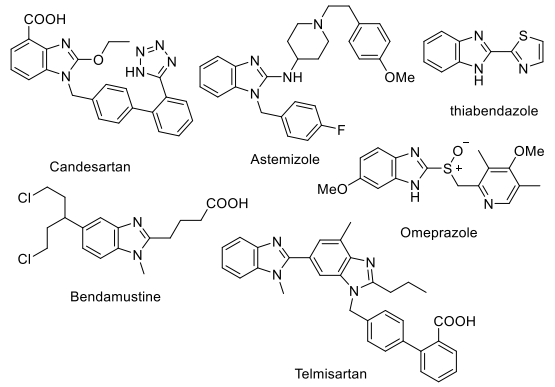


Figure 1. Representative pharmaceuticals containing a benzimidazole scaffold.

The use of ionic liquids as reaction media or catalysts for this protocol has also been widely investigated [14, 15]. However, the combination of microwave irradiation and ionic catalysis for benzimidazole synthesis, a green approach, is very limited in the literature. Herein, we report the ionic liquid-catalyzed, microwave-assisted synthesis of 1,2-disubstituted benzimidazoles from 1,2-diaminobenzenes and aldehydes. Benzimidazole derivatives were obtained in good to excellent yields in a short reaction time and under environmentally benign conditions. The ionic liquid [Bmim]BF_4 was efficiently used for the synthesis of 1,2-disubstituted benzimidazoles from benzylamines and *N*-monosubstituted-*o*-phenylenediamines [14].

2. Methodology

2.1. General Information

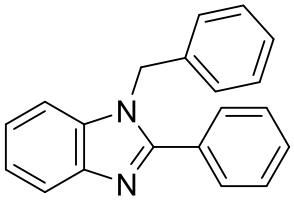
All 1,2-diaminobenzene derivatives, aldehydes, and the ionic liquid were purchased from the Sigma-Aldrich company. Microwave reactions were performed in a CEM microwave reactor at 50 °C, 120 W in a 3 mL capped vial. Column chromatography was performed using Merck silica gel (40-63 μM) packed by the slurry method under positive air pressure. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova NMR Spectrometer (^{1}H NMR running at 500 MHz and ^{13}C NMR running at 125 MHz) instrument. $CDCl_3$ (or CD_3OD, DMSO-D_6) was used as the NMR solvent. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant, and assignment. Data for ^{13}C NMR are reported regarding chemical shift (δ ppm).

2.2. General Procedure for the Benzimidazole Synthesis

Phenylenediamine (2 mmol, one equiv) was placed in a microwave vial. The corresponding aldehyde (4.4 mmol, 2.2 equiv) and [Bmim]BF_4 (0.2 mmol, 0.1 equiv) then were added. The reaction mixture was stirred under microwave irradiation (initial setting at 120W) for 5 minutes at 50 °C. The resulting mixture was purified using column chromatography (Eluent: *n*-hexane/EtOAc) to give the desired product.

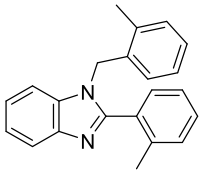
2.3. Supplementary Data

1-benzyl-2-phenyl-1*H*-benzo[*d*]imidazole (3a).



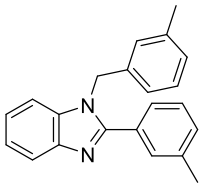
528 mg, 93% yield, white solid, **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.73-7.67 (m, 2H), 7.51-7.43 (m, 3H), 7.37-7.29 (m, 4H), 7.26-7.19 (m, 2H), 7.11 (d, *J* = 7.0 Hz, 2H), 5.47 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.3, 143.2, 136.6, 136.1, 130.1, 129.4, 129.2, 128.9, 127.5, 127.9, 126.2, 123.2, 122.8, 120.2, 110.6, 48.5. These NMR data are consistent with the literature report [16].

1-(2-methylbenzyl)-2-(*o*-tolyl)-1*H*-benzo[*d*]imidazole (3b).



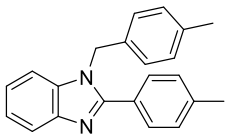
555 mg, 89% yield, white solid, **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.39-7.11 (m, 10H), 7.05-7.00 (m, 1H), 6.64 (d, *J* = 7.5 Hz, 1H), 5.19 (s, 2H), 2.25 (s, 3H), 2.15 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.9, 142.9, 138.5, 135.1, 134.9, 134.1, 130.7, 130.5, 129.9, 129.9, 129.8, 127.7, 126.4, 126.2, 125.7, 123.1, 122.5, 120.1, 110.6, 45.9, 19.9, 19.2. These NMR data are consistent with the literature report [17].

1-(3-methylbenzyl)-2-(*m*-tolyl)-1*H*-benzo[*d*]imidazole (3c).



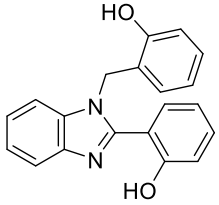
586 mg, 94% yield, white solid, **^{1}H NMR** (500 MHz, CD_3OD) δ 7.75 (d, *J* = 8.0 Hz, 1H), 7.48-7.17 (m, 8H), 7.09 (d, *J* = 4.0 Hz, 2H), 6.95 (dd, *J* = 7.5, 4.0 Hz, 1H), 6.51 (d, *J* = 7.5 Hz, 1H), 5.27 (s, 2H), 2.09 (s, 3H), 2.05 (s, 3H); **^{13}C NMR** (125 MHz, CD_3OD) δ 155.1, 143.2, 139.5, 136.5, 136.3, 135.4, 131.7, 131.4, 130.9, 130.8, 128.7, 128.6, 127.2, 126.9, 126.7, 124.4, 123.9, 119.9, 112.1, 46.6, 19.7, 19.0. These NMR data are consistent with the literature report [18].

1-(4-methylbenzyl)-2-(*p*-tolyl)-1*H*-benzo[*d*]imidazole (3d).



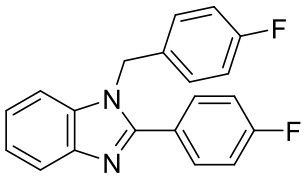
592 mg, 95% yield, brown solid, **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.35-7.31 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.23 (dt, *J* = 8.5, 4.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 5.43 (s, 2H), 2.42 (s, 3H), 2.35 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.1, 142.4, 140.5, 137.6, 135.9, 133.3, 129.8, 129.5, 129.2, 126.6, 125.9, 123.1, 122.8, 119.7, 110.7, 48.3, 21.5, 21.2. These NMR data are consistent with the literature report [19].

2-(1-(2-hydroxybenzyl)-1*H*-benzo[*d*]imidazol-2-yl)phenol (3e).



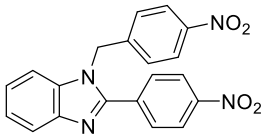
569 mg, 90% yield, white solid, **^{1}H NMR** (500 MHz, DMSO-D6) δ 11.05 (s, 1H), 9.92 (s, 1H), 7.71 (dd, *J* = 6.5, 1.7 Hz, 1H), 7.48 – 7.30 (m, 4H), 7.28 – 7.15 (m, 2H), 7.03 (t, *J* = 6.0 Hz, 2H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.58 (t, *J* = 7.5 Hz, 1H), 6.38 (d, *J* = 7.5 Hz, 1H), 5.40 (s, 2H); **^{13}C NMR** (1255 MHz, DMSO-D6) δ 156.4, 154.4, 152.1, 141.9, 135.2, 131.5, 130.3, 128.3, 126.7, 122.7, 122.5, 122.0, 119.1, 119.0, 118.7, 116.4, 116.2, 115.1, 110.9, 43.2. These NMR data are consistent with the literature report [20].

1-(4-fluorobenzyl)-2-(4-fluorophenyl)-1*H*-benzo[*d*]imidazole (3f).



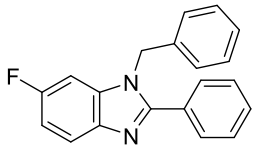
550 mg, 86% yield, white solid, **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88-7.84 (m, 1H), 7.64 (dd, *J* = 9.0, 5.5 Hz, 2H), 7.33 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.26 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 2H), 7.22-7.19 (m, 1H), 7.15 (t, *J* = 8.5 Hz, 2H), 7.08-6.99 (m, 4H), 5.40 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.1 (d, *J* = 188.0 Hz), 162.1 (d, *J* = 184.0 Hz), 153.2, 143.2, 136.0, 132.0, 131.3, 127.7, 126.3, 123.4, 123.0, 120.2, 116.3, 116.1, 110.4, 47.8. These NMR data are consistent with the literature report [21].

1-(4-nitrobenzyl)-2-(4-nitrophenyl)-1*H*-benzo[*d*]imidazole (3g).



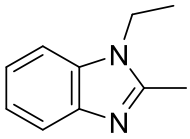
636 mg, 85% yield, white solid, **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.37-8.31 (m, 2H), 8.27-8.22 (m, 2H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 9.0Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 1H), 5.60 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 151.3, 148.8, 148.0, 142.8, 135.9, 135.6, 130.2, 126.9, 126.8, 124.8, 124.7, 124.3, 124.0, 120.8, 110.4, 48.2. These NMR data are consistent with the literature report [17].

1-benzyl-6-fluoro-2-phenyl-1*H*-benzo[*d*]imidazole (3h).



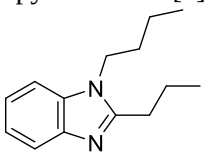
574 mg, 85% yield, white solid, **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 9.0, 5.0 Hz, 1H), 7.69-7.66 (m, 2H), 7.50-7.43 (m, 3H), 7.37-7.31 (m, 3H), 7.09 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.06 (ddd, *J* = 9.5, 9.0, 2.5 Hz, 1H), 6.88 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.42 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 159.9 (d, *J* = 240 Hz), 154.9, 139.3, 136.2, 135.8, 130.2, 129.7, 129.3, 129.3, 128.9, 128.1, 126.0, 120.7, 111.3, 97.4, 48.7. These NMR data are consistent with the literature report [22].

1-ethyl-2-methyl-1*H*-benzo[*d*]imidazole (3i).



250 mg, 78% yield, brown liquid, **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73-7.68 (m, 1H), 7.33-7.30 (m, 1H), 7.26 - 7.23 (m, 2H), 4.18 (q, *J* = 7.5 Hz, 2H), 2.63 (s, 3H), 1.42 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 151.1, 134.7, 122.9, 122.1, 119.1, 109.2, 38.7, 15.6, 13.8. These NMR data are consistent with the literature report [23].

1-butyl-2-propyl-1*H*-benzo[*d*]imidazole (3j).



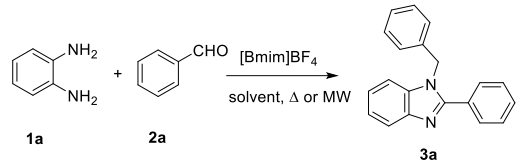
350 mg, 81% yield, white solid, **^{1}H NMR** (500 MHz, CD_3OD) δ 7.57 (dd, *J* = 6.5, 2.5 Hz, 1H), 7.43 (dd, *J* = 6.5, 2.0 Hz, 1H), 7.31 – 7.14 (m, 2H), 4.20 (t, *J* = 7.5 Hz, 2H), 2.88 (t, *J*= 7.5 Hz, 2H), 1.96-1.83 (m, 2H), 1.83-1.71 (m, 2H), 1.47-1.31 (m, 2H), 1.05 (t, *J* = 7.5 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (125 MHz, CD_3OD) δ 156.5, 143.0, 136.0, 123.4, 123.1, 118.9, 111.1, 44.4, 33.1, 29.9, 22.3, 21.1, 14.2, 14.1. These NMR data are consistent with the literature report [21].

3. Results and Discussion

Our initial efforts focused on optimizing conditions through variation of reaction parameters using the reaction of phenylenediamine with benzaldehyde. When a solution of 1,2-diaminobenzene **1a** (2 mmol) and benzaldehyde **2a** (4.4 mmol, 2.2 equiv)) in various solvents (6 mL) was stirred in the presence of $[Bmim]BF_4$ in 4 h, different yields of product 3a were observed. The results are summarized in Table 1. When the reaction proceeded in toluene at room temperature (RT) with 20 mol% of catalyst, a low yield of 1-benzyl-2-phenylbenzimidazole (**3a**) was obtained (Table 1, entry 1). Increasing the reaction temperature to 50°C led to the formation of benzimidazole derivatives in 39% yield (Table 1, entry 2). Under these reaction conditions, various solvents were also investigated. In acetonitrile, methanol, and ethyl acetate, product **3a** was isolated in moderate yields (Table 1, entry 3, 4, 8), while better yields were achieved with the use of ethanol, 2-propanol, and PGE-400 as solvents (Table 1, entries 5, 6, 7). In the case of PGE-400, this reaction solvent can be reused three times without significant activity loss (Table 1, entry 7). Interestingly, the yield of **3a** was slightly improved under solvent-free conditions

(Table 1, entry 9). Increasing the reaction temperature to 70 °C did not result in any improvement (Table 1, entry 10). Surprisingly, reducing the amount of catalyst to 10 mol% did not affect the reaction yield **3a** (Table 1, entry 11). To our delight, the reaction proceeded smoothly and efficiently under microwave irradiation. 93% yield of **3a** was furnished after 5 minutes of irradiation without using a solvent (Table 1, entry 12). This is our optimal conditions for the synthesis of 1,2-disubstituted benzimidazoles.

Table 1. Optimization of reaction conditions for the synthesis of 2-phenyl-1-benzyl-1*H* benzimidazole

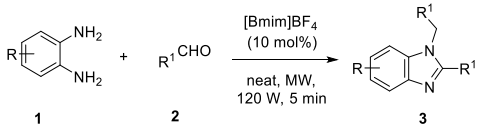


Entry	Solvent	Catalyst (mol%)	Temperature (°C)	Yield of 3a (%)[a]
1	PhMe	20	RT	17
2	PhMe	20	50	39
3	MeCN	20	50	64
4	MeOH	20	50	78
5	EtOH	20	50	82
6	*i*PrOH	20	50	81
7	PEG-400	20	50	85, 84, 83[b]
8	EtOAc	20	50	73
9	None	20	50	87
10	None	20	70	87
11	None	10	50	87
12	None	10	50	93[c]

[a]Isolated yield.
[b]Yields for 1[sr], 2[nd], 3[rd] run, respectively.
[c]Microwave-assisted synthesis at 120 W, 5 min.

With the optimal conditions in hands, we extended our studies to various aldehydes with substituted benzene 1,2-diamines under optimized conditions. In all cases, reactions were completed within 5 minutes, providing products with good to excellent yields (Table 2). The results are shown in Table 2. An array of aromatic aldehydes with either electron-donating (methyl, hydroxy) or electron-withdrawing (fluoro, nitro) groups are well tolerated in these reaction conditions. The aldehydes with electron-donating groups show slightly higher reaction activity than that with electron-withdrawing groups (Table 2, entry 2-7). The substrate with Me at the *ortho*-position gave the products in lower yield than those with Me at the *meta*-position and the *para*-position (Table 2, entry 2-4), presumably due to steric hindrance. The diamines with the electron-withdrawing group provided products with slightly better yields (Table 2, entry 8). The procedure is also suitable for non-aromatic aldehydes; products were obtained in good yield (Table 2, entries 9, 10). A large excess of the aldehyde was used for acetaldehyde because this chemical is highly volatile. In a previous study, high yields of benzimidazoles were also by using a combination of microwave irradiation and [bnmim]HSO_4 ionic liquid catalyst, but higher catalyst loading was required [24].

Table 2. Microwave-assisted synthesis of 1,2-disubstituted benzimidazoles using [Bmim]BF_4 catalyst



Entry	R	R^1	Products	Yield of 3 (%)[a]
1	H	Ph	3a	93
2	H	2-Me-Ph	3b	89
3	H	3-Me-Ph	3c	94
4	H	4-Me-Ph	3d	95
5	H	2-OH-Ph	3e	90

6	H	4-F-Ph	3f	86
7	H	4-NO_2-Ph	3g	85
8	3-F	Ph	3h	95
9	H	Me	3i	78[b]
10	H	Pr	3j	81

[a]Isolated yield.
[b]4 equivalent of aldehyde was used.

4. Conclusion

In summary, we have established an efficient and rapid approach to access 1,2-disubstituted benzimidazoles from 1,2-diaminobenzenes and aldehydes. The solvent-free and [Bmim]BF_4-catalyzed reaction was performed under microwave irradiation. The synthesis is suitable for both aryl and acyclic aldehydes. Attractive features of the synthesis include short reaction time, environmentally benign conditions, simple work-up procedure, and high efficiency. In the future, more substrates with substituents at 1,2-diaminobenzenes will be examined to expand the synthesis scope.

Acknowledgements

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