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MICROWAVE-ASSISTED, [BMIM]HSO_4-CATALYZED SYNTHESIS OF TETRASUBSTITUTED IMIDAZOLES VIA FOUR-COMPONENT REACTION

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Abstract. Imidazole derivatives are one of the most important classes of nitrogen-containing five-membered heterocycles with a wide range of biological activities. Thus, the synthesis of these heterocycles has attracted intensive research interest. The classical Debus–Radziszewski reaction is one of the most facile and straightforward methods to synthesize 2,4,5-trisubstituted imidazoles and 1,2,4,5-tetrasubstituted imidazoles. Various catalysts have been developed for this synthesis to improve efficiency and reduce environmental pollution. Ionic liquids, green solvents for synthesis, have also been employed for this synthesis. Furthermore, the use of microwave irradiation, which can bring many advantages such as: high yield of products, simple work-up, improved selectivity, and clean reaction pathways, has also investigated for this method. Herein, we described the synthesis of tetrasubstituted imidazoles under microwave irradiation. The four-component reaction of benzil, aryl aldehyde, ammonium acetate, and primary amine was performed using ionic liquid [Bmim]HSO_4 as the catalyst. Ten imidazole derivatives were furnished in high yield using an environmentally benign procedure. All of products were formed in a short time and simply purified by filtration and crystallization. Structures of all synthesized compounds were characterized by ^{1}H and ^{13}C NMR data analysis and by comparison with reported data. Interestingly, some synthesized compounds have been reported to possess antifungal activity on some fungi.

Keywords: Ionic liquid, Debus–Radziszewski reaction, aryl aldehyde, substituted imidazole.

Classification numbers: 1.1.3, 1.1.6, 1.2.5.

1. INTRODUCTION

Imidazole derivatives are one of the most important classes of nitrogen-containing five-membered heterocycles. They are an essential component of various biologically and pharmaceutically important compounds, including histidine, histamine, and biotin. Imidazole derivatives possess a wide range of biological activities [1, 2] including several well-known drugs in the market such as ketoconazole, omeprazole, cimetidine, etomidate, olmesartan, losartan, nilotinib, and tipifarnib. In addition, imidazolium salts have been well used as ionic liquids [3, 4]. On the other hand, imidazole derivatives possess good photophysical properties, which result in their potential in material chemistry application such as organic

electroluminescent devices (OLED) [5, 6]. Some imidazole derivatives were utilized as ligands in the metal-catalyzed reactions [7, 8]. Recent advances in green chemistry and organometallic catalysis have extended the utilization of imidazoles *N*-heterocyclic carbenes [9].

The classical Debus–Radziszewski reaction of 1,2-diketone, an aldehyde and an ammonia is one of the most facile and straightforward methods to synthesize 2,4,5-trisubstituted imidazoles [10, 11]. 1,2,4,5-Tetrasubstituted imidazoles could be obtained following this method by using a mixture of ammonia and a primary amine. Various catalysts have been developed for this four-component reaction, such as $BF_3.SiO_2$, L-proline, $HClO_4$–SiO_2, heteropolyacid, sodium benzenesulfonate, and molecular iodine [12, 13]. Ionic liquids, green solvents for synthesis, have also been employed for this synthesis [14].

Microwave-assisted organic synthesis results in spectacular acceleration of many chemical reactions as a consequence of three-dimensional heating of the reaction mass, which cannot be reproduced by classical heating methods. High yields, simple work-up, improved selectivity and clean reaction pathways are additional advantages of this synthetic technique [15]. Moreover, even reactions that do not occur with conventional heating can be performed with microwave irradiation. In most cases, microwave irradiation coupled with solvent-free techniques represents a powerful, eco-friendly, green alternative to conventional synthesis. In this article, we reported the synthesis of tetrasubstituted imidazoles by the four-component reaction of benzil, an aldehyde, an ammonia, and a primary amine using $[Bmim]HSO_4$ as a catalyst under microwave irradiation. Previously, this ionic liquid was used as a catalyst for imidazole synthesis [16], but this is the first time the four-component Debus–Radziszewski reaction is performed under microwave irradiation in combination with $[Bmim]HSO_4$ catalyst. The main advantages of the synthesis include: solvent-free and metal-free conditions, short reaction time, broad substrate scope, simple product purification, and high yield of products.

2. MATERIALS AND METHODS

2.1. Experimental section

2.1.1 General procedure

All aldehydes, amines, benzil, and the ionic liquid $[Bmim]HSO_4$ were purchased from Sigma-Aldrich company. Microwave reactions were performed in a CEM microwave reactor at 80 °C, 100 W in a 3 mL capped vial. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova NMR Spectrometer (^1H NMR running at 500 MHz and ^{13}C NMR running at 125 MHz). $CDCl_3$, CD_3COCD_3, and DMSO-d_6 were used as the NMR solvents.

General procedure for the synthesis of imidazoles: A mixture of benzil (1 mmol), aryl aldehyde (1 mmol, 1 equiv.) was placed in a 3 mL microwave vial. Ammonium acetate (1.05 mmol, 1.05 equiv.), amine (1 mmol, 1 equiv.) and $[Bmim]HSO_4$ (0.1 mmol, 0.1 equiv.) were added consecutively. The reaction mixture was allowed to stir under microwave irradiation (initial setting at 80 °C, 100 W) for 10 minutes. After completion of the reaction, the reaction mixture was cooled to room temperature and then diluted with water. The precipitate was filtered off and the filtrate was recrystallized from ethanol to obtain the desired product. Reaction yields were calculated based on weight of products after recrystallization. NMR data of all the synthesized compounds are consistent with the literature reports [17 - 22].

2.1.2 NMR data for synthesized compounds

1-benzyl-4,5-diphenyl-2-(p-tolyl)-imidazole (5a)

Pale yellow solid, 376 mg, 94 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 7.0 Hz, 2H), 7.59 (d, *J* =8.0 Hz, 2H), 7.34 (m, 3H), 7.27 -7.21 (m, 9H), 7.17 (t, *J* = 7.0 Hz, 1H), 6.88 –6.82 (m, 2H), 5.13 (s, 2H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 148.2,138.8, 138.0, 137.7, 134.6, 131.8, 131.15, 131.10, 129.9, 129.3, 129.0, 128.8, 128.6,128.1, 128.05, 127.3, 126.8, 126.3, 126.0, 48.3, and 21.4.

1-benzyl-2-(4-chlorophenyl)-4,5-diphenyl-imidazole (5b)

White solid; 399 mg, 95 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.57 (dd, *J* = 8.0, 4.5 Hz, 4H), 7.33 (t, *J* = 8.0 Hz, 5H), 7.25-7.08 (m, 8H), 6.85-6.75 (m, 2H), 5.07 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 146.9, 138.3, 137.3, 135.0, 134.3, 131.0, 130.8, 130.4, 130.3, 129.4, 128.9, 128.87, 128.81, 128.75, 128.2, 127.5, 126.8, 126.5, 125.9, and 48.3.

4-(1-benzyl-4,5-diphenyl-imidazol-2-yl)-*N*,*N*-dimethylaniline (5c)

White solid, 395 mg, 92 %. ^{1}H-NMR (500 MHz, DMSO-d6) δ: 7.59 (dd, *J* = 1.5, 8.5 Hz, 2H), 7.56 (dd, *J* = 2,5 Hz, 2H), 7.34-7.14 (m, 11H), 6.87 (t, *J* = 8.0 Hz, 2H), 6.73 (dt, *J* = 3.0 Hz, 2H), 5.17 (s, 2H, -CH_2), 3.00 (s, 6H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 150.8, 148.8, 137.9, 131.3, 131.26. 131.23, 131.1, 129.4, 129.38, 128.53, 128.5, 128, 127.2, 127.17, 126.93, 126.9, 126, 112, 100, 48.3, and 40.3.

1-benzyl-2-(4-nitrophenyl)-4,5-diphenyl-imidazole (5d)

White solid, 414 mg, 96 %. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.26 (dt, *J* = 3.0 Hz, 2H), 7.87 (dt, *J* = 2.5 Hz, 2H) 7.60 (d, *J* = 7.5 Hz, 2H), 7.43-7.19 (m, 11H), 6.89 (d, *J* = 6.0 Hz, 2H), 5.19 (s, 2H, -CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 147.6, 145.4, 139.3, 137, 136.9,133.9, 131.8, 131, 130.3, 129.3, 129.1, 129, 128.9, 128.83, 128.2, 127.8, 126.8, 125.7, 123.9, and 48.6.

2-(benzo[d][1,3]dioxol-5-yl)-1-benzyl-4,5-diphenyl-imidazole (5e)

White solid, 396 mg, 92 %. (500 MHz, DMSO-d_6) δ: 7.85 (dd, *J* = 1.5, 8 Hz, 2H), 7.36-7.12 (m, 13H), 6.83 (dt, *J* = 1.5, 8.5 Hz, 3H), 6.01 (s, 2H), 5.11 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 148.2, 147.8, 147.7, 137.8, 137.5, 134.4, 131.1, 129.9, 128.8, 128.8, 128.6, 128.1, 126.83, 126.8, 126.3, 126, 124.8, 123.1, 109.8, 108.4, 101.3, and 48.3.

2-(4-methoxyphenyl)-1,4,5-triphenyl-imidazole (5f)

Cream solid, 354 mg, 88 %. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.63 (d, *J* = 7.5 Hz, 2H), 7.39 (dd, *J* = 2.0, 8.5 Hz, 2H), 7.30-7.06 (m, 13H), 6.79 (dd, *J* = 2.0, 8.5 Hz, 2H), 3.80 (s, 3H, -CH_3O); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 159.6, 146.9, 138, 137.3, 134.5, 131.2, 130.8, 130.3, 130.3, 128.5, 128.3, 128.1, 127.4, 126.5,123.1, 113.6, and 55.2.

N,N-dimethyl-4-(1,4,5-triphenyl-imidazol-2-yl)aniline (5g)

White solid, 369 mg, 89 %. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.64 (d, *J* = 8.0 Hz, 2H), 7.32-7.08 (m, 15H), 6.59 (dd, *J* = 2.0, 9.5 Hz, 2H), 2.96 (s, 6H N-CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 150.1, 147.6, 137.54, 137.5, 131.2, 130.9, 130.86, 129.93, 129.9, 128.86, 128.83, 128.3, 128.28, 128.13, 128.1, 128, 127.5, 126.5, 111.5, and 40.2.

3-(1,4,5-triphenyl-imidazol-2-yl)-1H-indole (5h)

Yellowish solid, 374 mg, 91 %. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.47 (dd, J = 2.5, 6.0 Hz), 8.43 (s, 1H), 7.73 (dd, J = 2.0, 7.0 Hz, 2H), 7.30-7.17 (m, 15H), 6.35 (d, J = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 143.6, 137.6, 137.4, 135.5, 134.8, 131.2, 131, 129,23, 129.2, 128.3, 128.27, 128.1, 128.07, 127.8, 127.2, 126.5, 126.4, 123.8, 122.7, 122.1, 120.7, 110.8, and 107.

2-(2-nitrophenyl)-1,4,5-triphenyl-imidazole (5i)

White solid, 367 mg, 88 %. ^{1}H NMR (500 MHz, CD_3COCD_3) δ: 7.98 (d, 1H, J = 6.5Hz), 7.69-7.54 (m, 5H), 7.33-7.19 (m, 13H); ^{13}C NMR (125 MHz, DMSO-d6) δ: 148.7, 142.2, 136.8, 134.8, 133.6, 132.6, 132.3, 131.7, 130.5, 129.5, 128.6, 128.57, 128.2, 128.1, 127.8, 127.7, 126.6, 126.2, 125.9, 124.8, and 123.8.

2-(2,4-dichlorophenyl)-1,4,5-triphenyl-imidazole (5j)

White solid, 383 mg, 87 %. ^{1}1H NMR (500 MHz, CD_3COCD_3) δ: 7.59-7.58 (m, 3H), 7.50 (s, 1H), 7.41 (d, J=7.5 Hz, 1H), 7.33-7.17 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 143.9, 138.2, 136.0, 135.8, 135.5, 134.1, 133.6, 130.9, 130.2, 129.9, 129.4, 129.3, 128.6, 128,57, 128.4, 128.1, 128.0, 127.7, 127.4, 126.8, and 126.7.

4-(1-(3-chlorophenyl)-4,5-diphenyl-imidazol-2-yl)phenol (5k)

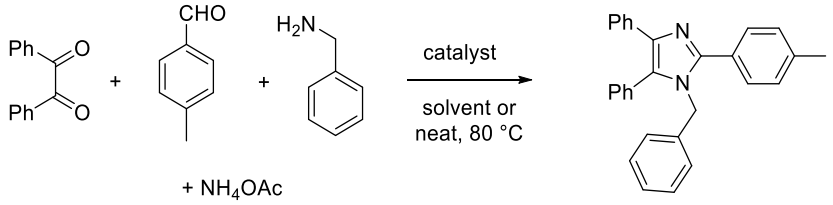
White solid, 363 mg, 86 %. ^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.99 (d, J = 6.5 Hz, 1H), 7.66-7.51, (m,3H), 7.34-7.23 (m,11H), 6.94 (d, J = 7.5 Hz, 1H), 6.78 (d, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d6) δ: 157.7, 146.5, 138.2,136.5, 134.4, 133.1, 131.2, 130.6, 130.5, 130.4, 129.9, 128.8, 128.7, 128.5, 128.4 128.1, 127.7,126.4, 126.3, 121.0, and 115.1.

3. RESULTS AND DISCUSSION

Our preliminary investigation began with the reaction of benzil (210 mg, 1 mmol), 4-methylbenzaldehyde (120 g, 1 mmol), ammonium acetate (82 g, 1.05 mmol), and benzyl amine (107 mg, 1 mmol) in the presence of different catalysts (20 mol%) in different solvents at 80 °C. The effect of solvent, catalyst, and reaction time on reaction yield was investigated and the results were summarized in Table 1.

Initially, ethanol was chosen as the medium for the reaction. As can be seen from Table 1, the product was provided in moderate yields using iodine and *L*-proline catalysts (Table 1, entries 1 and 2). In subsequent experiments, four different ionic liquids were employed as catalysts for the four-component reaction. The use of [Bpy]BF_4 gave the desired product in modest yield (Table 1, entry 4). Better yields were obtained when ionic liquids [Emim]OAc and [Hmim]HSO_4 were used (Table 1, entries 3 and 5). To our delight, under [Bmim]HSO_4 catalysis, product **3a** was isolated in excellent yield (Table 1, entry 6). Then, the reaction with [Bmim]HSO_4 catalyst was performed under solvent-free conditions and it furnished a product with 91 % yield within 2 h (Table 1, entry 7). In view of more environmentally friendly practice, the reaction was performed in a microwave reactor. With the same parameters as entry 7, the product was afforded with 94 % yield within only 10 minutes of irradiation (Table 1, entry8). Decreasing the quantity of [Bmim]HSO_4 catalyst to 10 mol% did not lower the reaction yield (Table 1, entry 9). Thus, our optimized conditions include solvent-free conditions, 10 minutes of irradiation in a microwave reactor at 100 W and 80 °C, and 10 mol% of ionic liquid [Bmim]HSO_4 catalyst.

Table 1. Optimization of reaction conditions for the synthesis of imidazoles.

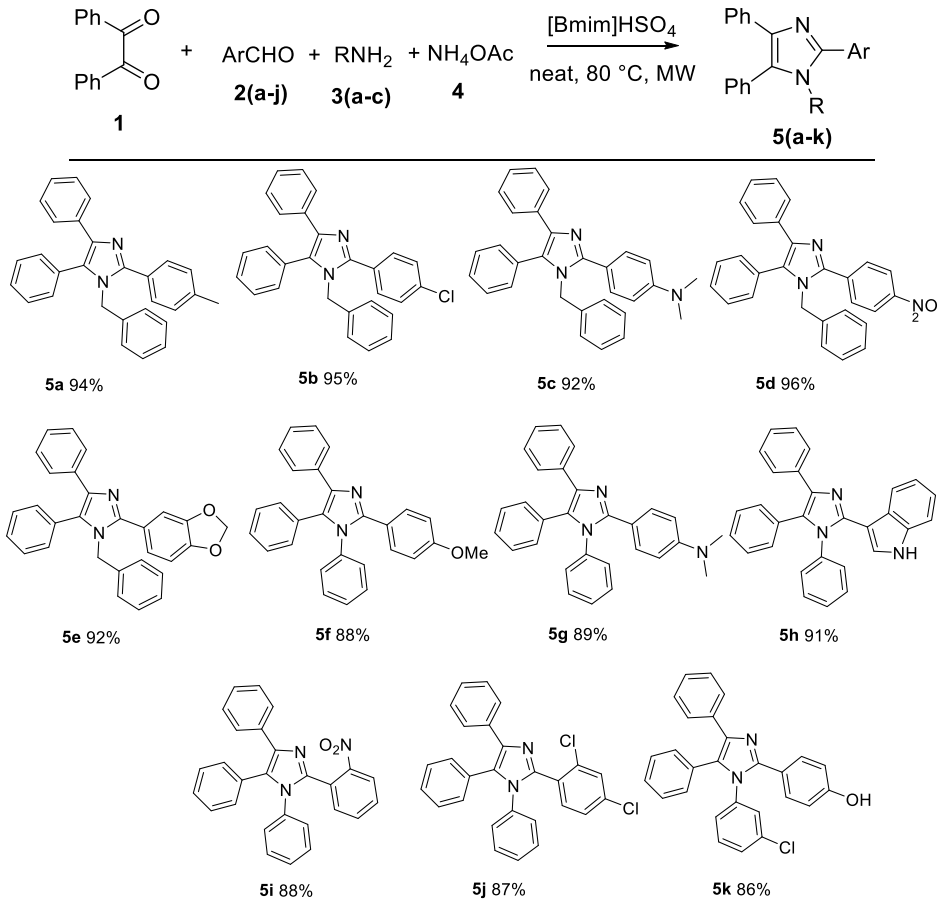


Entry	Catalyst (amount)	Solvent	Time	Temperature (°C)	Yield (%)[a]
1	Iodine	EtOH	24 h	80	72
2	*L*-proline	EtOH	24 h	80	74
3	[Emim]OAc	EtOH	12 h	80	84
4	[Bpy]BF_4	EtOH	36 h	80	68
5	[Hmim]HSO_4	EtOH	5 h	80	86
6	[Bmim]HSO_4	EtOH	5 h	80	90
7	[Bmim]HSO_4	none	2 h	80	91
8	[Bmim]HSO_4	none	10 min	80	94[b]
9	[Bmim]HSO_4	none	10 min	80	94[c]

a: isolated yield; b: reaction was performed in a microwave reactor; c: reaction was performed in a microwave reactor and 10 mol% of catalyst was used.

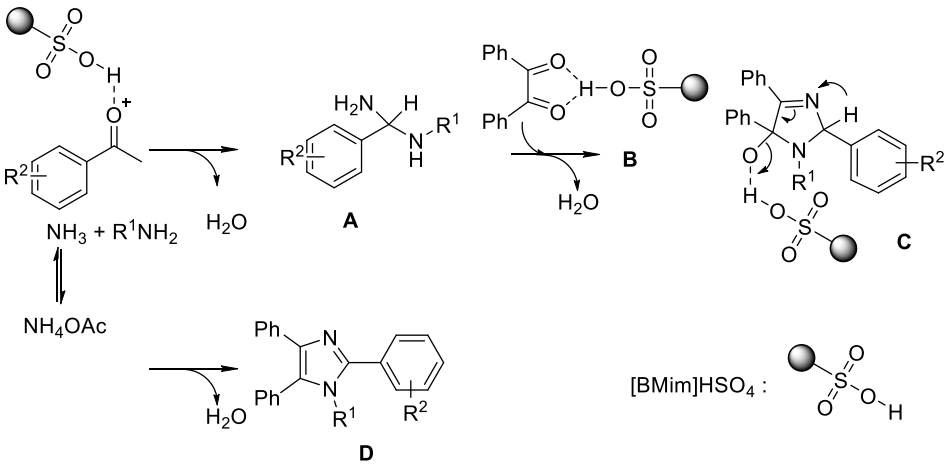
Having optimized conditions in hand, we then examined the scope of the reaction for various aryl aldehydes (**2a**-**2j**) and amines (**3a**-**3c**). The results are presented in Figure 1 (**5a**-**5k**). As suggested, under the optimized conditions, reaction conditions with different amines and aryl aldehydes all provided desired products in high yields. Electron-donating and electron-withdrawing groups in aryl aldehydes and amines afforded products without any difficulty. It has been observed that slightly better yields are achieved from aldehydes possessing electron withdrawing groups (**5b** and **5d**), while the presence of electron-donating groups slightly decreased reaction yields (**5c**, **5f**, **5g**, and **5k**). Aldehydes and amines with *ortho*-substituents gave slightly lower yields probably due to stearic hindrance (**5i** and **5j**). Noticeably, compounds **5f**, **5g**, **5i**, **5j**, and **5k** have been reported to possess antifungal activity on some fungi [23]. According to a report by Shekarchi, the synthesized compounds could be mutant isocitrate dehydrogenase 1 inhibitors [16].

The proposed mechanism of the formation of tetrasubstituted imidazoles *via* the four-component Debus–Radziszewski reaction under [Bmim]HSO_4 is described in Scheme 1. The role of the ionic liquid catalyst is to activate the aldehyde and the diketone. Initially, [Bmim]HSO4-activated aryl aldehyde reacts with ammonium acetate and an amine to generate a diamine intermediate **A**. This intermediate then reacts with [Bmim]HSO4-benzil **B** to form a ring intermediate **C**. Finally, dehydration of the intermediate **C** provides imidazole **D**.



Reaction conditions: **1** (1 mmol), **2** (1 mmol), **3** (1.05 mmol), **4** (1.05 mmol), and [Bmim]HSO_4 (0.1 mmol), a: isolated yield.

Figure 1. Examination of substrate scope.



Scheme 1. Proposed reaction mechanism for the formation of tetrasubstituted imidazoles.

4. CONCLUSIONS

In conclusion, in the present work we introduced a simple, efficient, and environmentally benign one-pot four-component method for the construction of 1,2,4,5-tetrasubstituted imidazoles in solvent-free conditions, catalyzed by the ionic liquid [Bmim]HSO_4. This microwave-assisted approach was successfully used to synthesize a variety of imidazole derivatives from aromatic aldehydes and benzyl amines or aromatic amines with good to excellent yields. In the future, other 1,2-diketones will be prepared and examined for this four-component reaction.

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CRediT authorship contribution statement. Author 1: Methodology, Investigation, Manuscript preparation, Data analysis. Author 2: Formal analysis, Experiment.

Declaration of competing interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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