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Minoo Dabiri [a], Peyman Salehi [b], Mostafa Baghbanzadeh [a] & Maryam Shakouri Nikcheh [a]
[a] Department of Chemistry, Faculty of Science, Shahid Beheshti University, G. C., Evin, Tehran, Iran
[b] Department of Phytochemistry, Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, Tehran, Iran
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Water-Accelerated Selective Synthesis of 1,2-Disubstituted Benzimidazoles at Room Temperature Catalyzed by Brønsted Acidic Ionic Liquid

Minoo Dabiri,[1] Peyman Salehi,[2] Mostafa Baghbanzadeh,[1] and Maryam Shakouri Nikcheh[1]

[1]Department of Chemistry, Faculty of Science, Shahid Beheshti University, G. C., Evin, Tehran, Iran

[2]Department of Phytochemistry, Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, Tehran, Iran

Abstract: An environmentally benign method for the rapid and selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles by the reaction of *o*-phenylenediamines and aromatic aldehydes in the presence of 1-methylimidazolium triflouroacetate ([Hmim]TFA) at room temperature under aqueous conditions is described. The ionic liquid is reusable and could be recycled for several runs without any decrease in its efficiency.

Keywords: Aldehyde, benzimidazole, heterocycle, ionic liquid, water

INTRODUCTION

Benzimidazole derivatives are an important structural element in medicinal chemistry and show a broad spectrum of pharmacological activities. Several compounds from this class have been used as antihistaminic, antiparasitic, antitumor, fungicide, immunosuppressant, antiviral, and anticonvulsant agents.[1–5] They have also been used as ligands for asymmetric

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Address correspondence to Minoo Dabiri, Department of Phytochemistry, Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, G. C., Evin, Tehran, Iran. E-mail: m-dabiri@sbu.ac.ir

catalysis.[6] Many methods have been reported for the synthesis of these heterocycles.[7–13] Among them, the condensation of 1,2-phenylenediamines with aldehydes followed by oxidation is a common method,[14–22] but the main problem of this method is the generation of 2-substituted and 1,2-disubstituted benzimidazoles with poor selectivity. However, the attempts to modify the reaction condition still suffer from some drawbacks such as using expensive and toxic reagent, a special oxidation process, tedious workup procedures, and long reaction times.

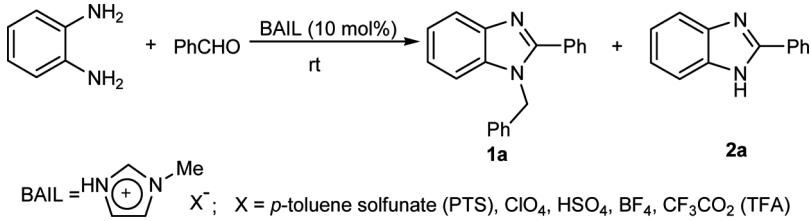
Ionic liquid (IL) technology, when used in place of classical organic solvents, may offer an environmentally benign approach toward modern synthetic chemistry.[23] The implementation of task-specific ionic liquids (TSILs) further enhances the versatility of classical ILs where both reagent and medium are coupled.[24] The union of reagent with medium has been found to be a viable alternative approach toward modern synthetic chemistry especially when considering the growing environmental demands being placed on chemical processes. Previous reports have documented the feasibility of the application and reuse of TSILs in classical organic processes.[25] A specific viewpoint focused on the use of Brønsted acid TSILs in modern synthetic chemistry.[26]

In continuation of our interest in finding new environmentally benign methods for the synthesis of heterocyclic compounds,[27–30] here we report a new procedure for the rapid and selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in the presence of 1-methylimidazoluim triflouroacetate ([Hmim]TFA)[31,32] as a Brønsted acidic ionic liquid (BAIL) at room temperature. We also show that in the presence of water an inconceivable decrease in the reaction time is observed.

RESULTS AND DISCUSSION

Our initial investigation focused on the use of ILs as the catalyst in the reaction of *o*-phenylenediamine and benzaldehyde under solvent-free conditions (Scheme 1). It is worth noting that ILs were dried carefully before use in the experiments.

The data collected in Table 1 indicated that despite the presence of 1-methylimidazolium *p*-toluenesulfonate ([Hmim]PTS) or 1-methylimidazolium perchlorate ([Hmim]ClO_4) the reaction did not occur to a significant extent within 12 h (Table 1, entries 1 and 2), 1-methylimidazolium hydrogen sulfate ([Hmim]HSO_4) gave the product **1a** in low yield and poor selectivity within the same reaction period (Table 1, entry 3). Further screening led to the observation that 1-methylimidazolium tetraflouroborate ([Hmim]BF_4) afforded **1a** in 65% yield after 5 h, but with a 80:20 ratio of **1a**/**2a** (Table 1, entry 4). Further efforts with



Scheme 1. Checking different BAILs in the synthesis of benzimidazoles.

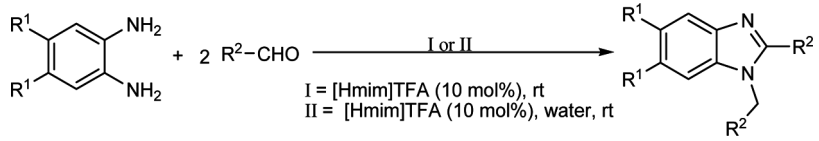
1-methylimidazolium triflouroacetate ([Hmim]TFA) afforded **1a** in 86% yield with no detectable production of **2a** (Table 1, entry 5). Also we found that the reaction ran in water rapidly with high selectivity (Table 1, entry 6). To evaluate the better catalytic activity of [Hmim]TFA, the reaction was run in the presence of 10 mol% triflouroacetic acid (TFA) under solvent-free and aqueous conditions and also in ethanol, and it clearly demonstrated that under this condition the selectivity and yield are not so good (Table 1, entries 7–9). Finally, acetic acid was checked as an acidic catalyst in reaction in ethanol and under solvent-free conditions, and it could be observed that no satisfactory results were obtained under these conditions (Table 1, entries 10, 11).

Encouraged by these results, the highly selective synthesis of other 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazole derivatives were conducted at room temperature using 10 mol% of [Hmim]TFA (Scheme 2). Similarly, various *o*-phenylenediamine ($R^1 = H$, Me, Cl) reacted with different

Table 1. Effect of different catalyst on the yield and selectivity in the reaction of *o*-phenylenediamine and benzaldehyde

Entry	Catalyst (10 mol%)	Solvent	Time (h)	Yield (%)	**1a**/**2a**[a]
1	[Hmim]PTS	—	12	NR	—
2	[Hmim]ClO_4	—	12	40	60/40
3	[Hmim]HSO_4	—	12	60	60/40
4	[Hmim]BF_4	—	5	75	80/20
5	[Hmim]TFA	—	3	86	99/1
6	[Hmim]TFA	Water	0.15	88	99/1
7	TFA	—	5	70	60/40
8	TFA	Water	1	82	90/10
9	TFA	Ethanol	2	76	80/20
10	CH_3COOH	Ethanol	2	76	80/20
11	CH_3COOH	—	12	NR	—

[a]The **1a**/**2a** ratio was determined by ^1H NMR analysis.



Scheme 2. Selective synthesis of 2-substituted benzimidazoles.

aromatic and hetero-aromatic aldehydes to afford the desired adducts in good yields (Table 2). In all cases, the reactions progressed smoothly at ambient temperature with excellent selectivities.

The organic reactions in aqueous media have attracted much attention in synthetic organic chemistry, not only because water is one of the most abundant, cheapest, and environmentally friendly solvents but also because water exhibits unique reactivity and selectivity, which is different from those conventional organic solvents.[33,34] In many reactions, significant rate enhancements are observed in water compared to organic solvents.[35]

When we conducted similar reactions in water, the expected products were obtained in good yields and selectivities and the reaction times became shorter than those in the first condition (Table 2). Several aromatic aldehydes carrying different functional groups and also heteroaromatic aldehydes (Table 2, **1i–k**) were used in reactions, and in all cases the desired products were obtained successfully. In addition to the previously mentioned advantages, the simple workup procedure makes this process environmentally friendly, as well as the easy purification, which requires only filtration of the products followed by recrystallization from ethanol.

To investigate the possibility of recycling the catalyst, an investigation was made of the reaction of *o*-phenylenediamine and benzaldehyde in the presence of 10 mol% of [Hmim]TFA in water. After completion of the reaction, the mixture was filtered to separate the product. After washing the BAIL with the appropriate solvent (for elimination of the unreacted starting products) and drying under high vacuum, the recycled IL was used for further runs. No decrease in catalytic activity of BAIL was observed even after four runs (Table 2, **1a**).

In conclusion, a simple, rapid, and environmentally friendly method for the selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles is described. In this new procedure, water accelerated the reaction of *o*-phenylenediamines and aromatic aldehydes in the presence of [Hmim]TFA, as a BAIL. Also the workup procedure is very simple, and chromatography is not required. Starting materials are inexpensive and

Table 2. Synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles

			IL		IL/water		Mp (°C)	
Product	R^1	R^2	Time (h)	Yield (%)[a]	Time (min)	Yield (%)[a]	Found	Reported[b]
1a	H	C_6H_5	3	86	10	88, 87, 88, 86[c]	132–133	132[22]
1b	H	2-ClC_6H_4	5	82	15	85	162–163	163–164[22]
1c	H	2-$MeOC_6H_4$	4	85	15	85	152–154	153[19]
1d	H	4-$Me_2NC_6H_4$	3	89	10	90	250–252	255–256[19]
1e	H	4-ClC_6H_4	4	93	15	92	135–136	136[19]
1f	H	4-MeC_6H_4	3.5	87	15	88	128–130	128–130[22]
1g	H	4-$MeOC_6H_4$	1	85	10	86	129–130	129–130[22]
1h	H	4-^{i}PrC_6H_4	2	88	10	87	176–177	176[22]
1i	H	2-Pyridyl	3	80	20	80	130–132	130–131[21]
1j	H	2-Furyl	4	78	20	81	93–95	94[21]
1k	Me	4-Pyridyl	5	78	20	76	164–166	—
1l	Me	4-HOC_6H_4	4	84	15	80	219–221	—
1m	Me	4-ClC_6H_4	3	89	15	86	190–191	190[22]
1n	Me	4-MeC_6H_4	3	90	15	95	176–177	177[22]
1o	Cl	4-HOC_6H_4	2	86	10	88	199–200	—

[a]Isolated yield.

[b]The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedures.

[c]IL was recycled for four runs.

commercially available. We hope that this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry programs.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9200 apparatus. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. The elemental analyses were performed with an Elementar Analysensysteme GmbH Vario EL CHNS mode. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz. All chemical reagents were obtained from Fluka and Merck and were used without purification.

General Procedure for the Synthesis of 2-Aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in [Hmim]TFA

Aldehyde (2 mmol) and *o*-phenylenediamine (1 mmol) were mixed with ionic liquid (0.02 g, 0.1 mmol) and placed in a round-bottomed flask. The mixture was stirred at room temperature. After the completion of the reaction as confirmed by thin-layer chromatography (TLC; eluent: *n*-hexane/ethyl acetate: 3/1), cold water was added, and the precipitated product was separated by simple filtration. Finally the crude product was recrystallized from ethanol.

General Procedure for the Synthesis of 2-Aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in Water in the Presence of [Hmim]TFA

[Hmim]TFA (0.02 g, 0.1 mmol), *o*-phenylenediamine (1 mmol), and aromatic aldehyde (2 mmol) were added to 2 mL of water, and the reaction was stirred in a round-bottomed flask for the appropriate time (see Table 2). After the completion of the reaction, the mixture was filtered, and the resulting crude product was recrystallized from ethanol.

Spectral Data for New Compounds

Compound **1l** ($C_{22}H_{20}N_2O_2$): IR (KBr) ν/cm^{-1}: 3500, 3440, 1615, 1513, 1280. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.27 (s, 3H, CH_3), 2.30

(s, 3H, CH_3), 5.34 (s, 2H, CH_2), 6.67 (s, 2H, Ar-H), 6.78–6.88 (m, 4H, Ar-H), 7.17 (s, 1H, Ar-H), 7.42–7.52 (m, 3H, Ar-H), 9.44 (s, 1H, OH), 9.97 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 20.3, 20.6, 47.3, 111.3, 115.9, 119.4, 121.4, 127.7, 130.6, 130.8, 131.1, 134.9, 141.7, 153.1, 157.0, 159.0. MS (EI, 70 eV) (m/z, %): 238 ($M^+ - 106$, 100), 223 (35), 119 (20), 78 (25), 51 (30). Anal. calcd. for $C_{22}H_{20}N_2O_2$ (344.41): C, 76.72; H, 5.85; N, 8.13%. Found: C, 76.64; H, 5.81; N, 8.23%.

Compound **1o** ($C_{20}H_{14}Cl_2N_2O_2$): IR (KBr) ν/cm^{-1}: 3558, 3405, 1611, 1513, 1280. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 5.45 (s, 2H, CH_2), 6.67 (d, $J = 8.3$ Hz, 2H, Ar-H), 6.81 (d, $J = 8.3$ Hz, 2H, Ar-H), 6.91 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.58 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.81 (s, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 9.47 (s, 1H, OH), 10.03 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 47.7, 113.0, 116.0, 116.1, 120.3, 124.9, 125.0, 127.0, 131.1, 136.0, 142.7, 156.4, 157.2, 159.7. MS (EI, 70 eV) (m/z, %): 345 (M^+, 5), 278 (100), 107 (20), 78 (25). Anal. calcd. for $C_{20}H_{14}Cl_2N_2O_2$ (385.24): C, 62.35; H, 3.66; N, 7.27%. Found: C, 62.28; H, 3.41; N, 7.23%.

Compound **1k** ($C_{20}H_{18}N_4$): IR (KBr) ν/cm^{-1}: 3436, 2921, 1685, 1603, 1475, 1450. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.33 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 5.71 (s, 2H, CH_2), 7.03 (s, 1H, Ar-H), 7.32–7.68 (m, 4H, Ar-H), 8.12 (s, 1H, Ar-H), 8.52–8.76 (m, 4H, Ar-H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 20.1, 20.4, 47.2, 111.3, 120.2, 123.3, 132.0, 132.4, 135.2, 137.9, 138.2, 141.6, 146.7, 148.0, 150.1, 150.4. MS (EI, 70 eV) (m/z, %): 314 (M^+, 100), 223 (80), 208 (40), 116 (20), 91 (25). Anal. calcd. for $C_{20}H_{18}N_4$ (314.38): C, 76.41; H, 5.77; N, 17.82%. Found: C, 76.40; H, 3.61; N, 17.63%.

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