Article

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[C_{12}mim]Br: A Temperature-dependent Phase Transfer Catalyst and Its Application for Aerobic Oxidative Synthesis of 2-Aryl Benzimidazoles, Benzoxazoles or Benzothiozoles Catalyzed by TEMPO Based Ionic Liquid

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The application of [C_{12}mim]Br ionic liquid/o-xylene temperature-dependent biphasic system into the [Imim-TEMPO][Cl]/O_2-promoted condensation between *o*-phenylenediamines, *o*-aminophenol or *o*-aminothiophenol with aldehydes for preparing benzimidazoles, benzoxazoles or benzothiozoles is described. Several aldehydes and *o*-phenylenediamines, *o*-aminophenol or *o*-aminothiophenol were reacted efficiently to form corresponding products in excellent yields. Both the [Imim-TEMPO][Cl] and [C_{12}mim]Br could be reused at least eight times without significantly decreasing the catalytic activity.

Keywords: Benzimidazoles; Benzoxazoles; Benzothiazoles; Aerobic oxidation; Temperature-dependent phase transfer catalyst.

INTRODUCTION

Over the past several decades, Benzimidazoles and their derivatives, known as an important class of N-containing heterocyclic compounds, have received considerable atention in recent years due to its possess significant pharmacological and biological activities, such as anticonvulsant, antianxiety, antiulcer, antihypertensive, antiviral, antifungal, anticancer, and antihistamine.[1-5] The excellent characterristics of benzimidazole derivatives have promoted extensive studies for their synthesis. Typically, there are two methods for the synthesis of benzimidazoles. The first is the condensation of *o*-phenylenediamine with carboxylic acids or their derivatives (nitriles, imidates, orthoesters) under harsh dehydrating conditions involving using strong acids and/or high temperatures.[6-10] The second is oxidative cyclo-dehydrogenation of aniline Schiff's base, which are often generated in situ from the condensation of *o*-phenylenediamines and aldehydes. Various oxidative reagents such as $Pb(OAc)_4$,[11] $Na_2S_2O_5$,[12] $(NH_4)_2S_2O_8$,[13] DDQ,[14] MnO_2,[15] Oxone,[16] H_2O_2,[17] have recently been reported. However, this method has some drawbacks involving requiring stoichiometric or excess amount of oxidants to be used, low yields, long reaction times, harsh reaction conditions, problematic by-products. In recent years, the use of molecular oxygen as an economic and green oxidant for the catalytic oxidative reactions has received much attention. The stable nitroxyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) has attracted considerable attention and been widely used to catalyze oxidative reaction of hydrocarbons, alcohols, and amines owing to its low toxicity, reversible redox behavior, and high efficiency and selectivity.[18] Chen and co-workers[19] reported aerobic oxidative synthesis of 2-substituted benzoxazoles, benzothiazoles, and benzimidazoles catalyzed by 4-methoxy-TEMPO. However, TEMPO is quite expensive. Therefore, its efficient recycling is highly desirable.

Recently, several strategies have emerged to conquer the problem of TEMPO recycling through the design of various types of supported TEMPO including mesoporous silica,[20] silica solgels,[21] cross-linked polystyrene resins,[22] which allowed the catalyst to be recycled out of the reaction media by simple filtration. However, owing to the heterogeneous nature of the reaction, most of these systems were far less versatile and efficient than homogeneous TEMPO. So a homogeneous system that contain TEMPO is in expectation.

[C_{12}mim]Br is a white powder at room temperature, and it is nearly insoluble in *o*-xylene, but miscible at 120 ^oC. So [C_{12}mim]Br exhibits a temperature-dependent phase behavior with *o*-xylene. Moreover, [Imim-TEMPO][Cl] powder is miscible in [C_{12}mim]Br at high temperature, but not soluble in *o*-xylene.

Herein, we report a new temperature-dependent biphasic system, including recoverable 1-dodecyl-3-methylimidazolium bromine([C_{12}mim]Br) ionic liquid and *o*-xylene, and its application in the synthesis of 2-aryl benzimidazoles, benzoxazoles, and benzothiazoles by *o*-phenylenediamines, *o*-aminophenol or *o*-aminothiophenol and al-

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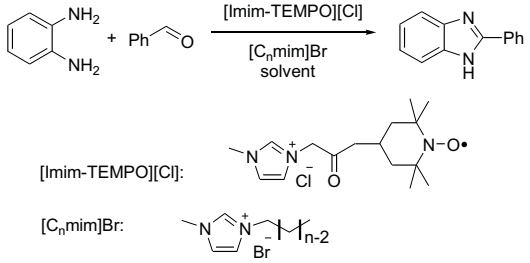
dehydes using [Imim-TEMPO][Cl] as catalyst and molecular oxygen as oxidant. On the basis of pioneering work, we explore the catalytic role of the [C_{12}mim]Br/*o*-xylene biphasic system in the reaction. To our delight, this system exhibited excellent catalytic activity and stability. In addition, the catalyst and [C_{12}mim]Br can be successfully recovered and reused.

RESULTS AND DISCUSSION

Initially, the reaction between *o*-phenylenediamine and benzaldehyde was selected for the aerobic oxidative synthesis of benzimidazole as a model reaction for optimizing the reaction conditions, and the results are summarized in Table 1. A variety of [$C_n$min]Br ionic liquids were then investigated in the reaction, showing varying activities in the reaction, among which [C_{12}min]Br was found to be the best one, giving the highest yield (entries 1-5). When in the absence of [C_{12}min]Br, the yield was very poor (entry 6). So [C_{12}min]Br was essential for the reaction. The screen of the loadings of [C_{12}mim]Br was then carried out, the result revealed that 2 mmol was the most suitable proportion, more loading could not enhance the product yield (entries 5, 7-9). Moreover, the loading of catalyst ([Imim-TEMPO][Cl]) was also tested, we found that 5 mol% was the most suitable proportion (entries 5, 10-11). The effect of solvent was also screened by using several solvents which could formed thermoregulated phase-transfer system with [C_{12}min]Br. We discovered that nonpolar aromatic solvents trate (entries 5, 12-13). In addition, temperature significantly affected the reaction, the phase transformation temperature is about 100 °C; when the temperature was lower than 80 °C, the low yield was obtained due to the system was not totally homogeneous, and it reached a maximum at 120 °C. These results show that the moderate temperature is 120 °C (entries 5, 14-16). Finally, we also tested the influence of the gas, and we found that the O_2 is significant for the reaction. When the reaction conducted under N_2, the reaction could not occurred (entries 5, 17).

Under the optimized conditions, the scope of the present transformation was extended to *o*-phenylenediamine with various substituted aromatic aldehydes, and the results are shown in Table 2. In most cases, *o*-phenylenediamine reacted with various aldehydes smoothly to give the corresponding products in excellent yields, regardless of the presence of electron-donating or electron-withdrawing functionalities. It seemed that benzaldehydes bearing electron-deficient aromatic rings at the para-position gave

Table 1. Optimization of the reaction conditions[a]

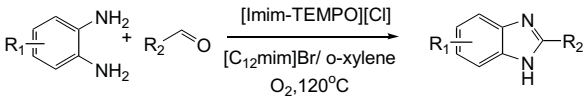


Entry	Catalyst (mol%)	Ionic liquid (mmol)	Solvent	T/	Gas	Yield (%)[b]
1	5	[C_4min]Br (2)	*o*-xylene	120	O_2	75
2	5	[C_6min]Br (2)	*o*-xylene	120	O_2	79
3	5	[C_8min]Br (2)	*o*-xylene	120	O_2	84
4	5	[C_{10}min]Br (2)	*o*-xylene	120	O_2	91
5	5	[C_{12}min]Br (2)	*o*-xylene	120	O_2	97
6	5	[C_{12}min]Br (0)	*o*-xylene	120	O_2	19
7	5	[C_{12}min]Br (0.5)	*o*-xylene	120	O_2	65
8	5	[C_{12}min]Br (1)	*o*-xylene	120	O_2	85
9	5	[C_{12}min]Br (3)	*o*-xylene	120	O_2	97
10	0	[C_{12}min]Br (2)	*o*-xylene	120	O_2	15
11	10	[C_{12}min]Br (2)	*o*-xylene	120	O_2	97
12	5	[C_{12}min]Br (2)	EtOAc	77	O_2	0
13	5	[C_{12}min]Br (2)	toluene	90	O_2	52
14	5	[C_{12}min]Br (2)	*o*-xylene	60	O_2	45
15	5	[C_{12}min]Br (2)	*o*-xylene	80	O_2	63
16	5	[C_{12}min]Br (2)	*o*-xylene	100	O_2	73
17	5	[C_{12}min]Br (2)	*o*-xylene	120	N_2	trace

[a] Reaction conditions: *o*-phenylenediamines (5 mmol) and benzaldehyde (5 mmol) were placed in a 30 mL three-necked flask containing 15 mL *o*-xylene. The reaction mixture was stirred at 120 °C for 0.5 h. Then [Imim-TEMPO][Cl] and [$C_n$min]Br were then added, and stirred at corresponding temperature under atmosphere for 4 h.
[b] Isolated yield.

higher yields than did those bearing electron-rich aromatic rings (entries 2-9). The reason may be that the strong electron-withdrawing groups (NO_2) enhanced the reaction rate due to the strong withdrawing ability of the group increase in electrophilicity of the carbonyl carbon (entries 6-8). The sterical hindrance of the substituted benzaldehydes also influenced the reaction. For example, the more sterically hindered ortho-chlorobenzyl benzaldehydes which had reaction with *o*-phenylenediamine furnished the target product in lower yield than para-chlorobenzyl benzaldehydes (entries 3, 4). Heteroaryl amines such as ortho-furyl aldehydes were used in the reaction, and the yields were satisfactory (entries 10, 11). In addition, 4-nitro-*o*-phenylenediamine was also employed in the reaction, and to our delight, it re-

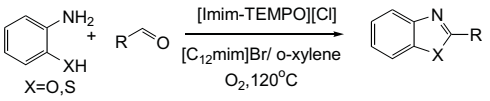
Table 2. Synthesis of 2-substituted benzimidazoles from various aromatic aldehydes[a]



Entry	R_1	R_2	Reaction time (h)	Yield (%)[b]
1	H	C_6H_5	4	97
2	H	4-BrC_6H_4	3	95
3	H	4-ClC_6H_4	3	95
4	H	2-ClC_6H_4	3.5	91
5	H	2, 4-ClC_6H_3	3.5	93
6	H	4-$NO_2C_6H_4$	3	96
7	H	4-$MeOC_6H_4$	3	94
8	H	4-$Me_2NC_6H_4$	4	90
9	H	3,4,5-$MeOC_6H_2$	4	93
10	H	2-Furyl	5	89
11	H	5-Methyl-2-Furyl	5	88
12	4-NO_2	Ph	5	93

[a] Reaction conditions: *o*-phenylenediamines (5 mmol) and benzaldehyde (5 mmol) were placed in a 30 mL three-necked flask containing 15 mL *o*-xylene. The reaction mixture was stirred at 120 °C for 0.5 h. Then 5 mol% [Imim-TEMPO][Cl] and 2 mmol [C_{12}min]Br were then added, and stirred at 120 °C under O_2 atmosphere for several hours.
[b] Isolated yield.

Table 3. Aerobic oxidative synthesis of benzoxazoles and benzothiazoles[a]



Entry	X	R	Reaction time (h)	Yield (%)[b]
1	O	Ph	4	88
2	O	4-ClC_6H_4	4	93
3	O	4-$CH_3OC_6H_4$	4.5	91
4	S	Ph	4	85
5	S	4-ClC_6H_4	4	87
6	S	4-$NO_2C_6H_4$	3.5	83

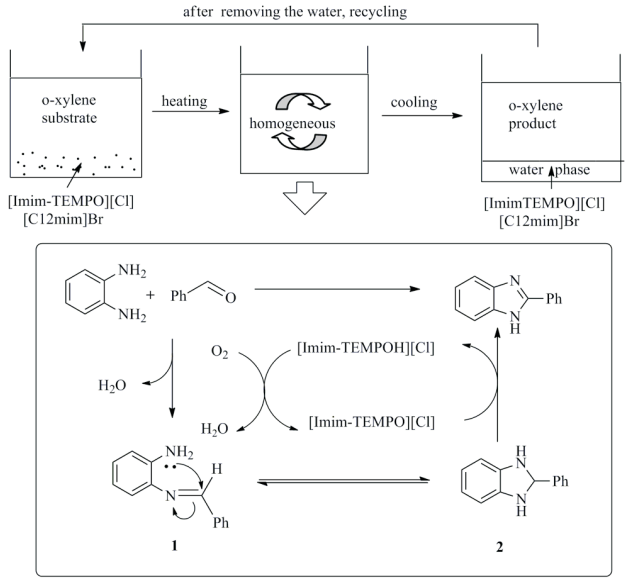
[a] Reaction conditions: 2-aminophenol or 2-amino-thiophenole (5 mmol) and benzaldehyde (5 mmol) were placed in a 30 mL three-necked flask containing 15 mL *o*-xylene. The reaction mixture was stirred at 120 °C for 0.5 h. Then 5 mol% [Imim-TEMPO][Cl] and 2 mmol [C_{12}min]Br were then added, and stirred at 120 °C under O_2 atmosphere for several hours.
[b] Isolated yield.

sulted in good yields (entry 12).

Having successfully achieved the synthesis of benzimidazoles, the [C_{12}mim]Br/*o*-xylene system was then expanded to catalyze the synthesis of benzoxazoles and benzothiazoles using *o*-aminophenol and *o*-aminothiophenol respecttively as the starting materials. As summarized in Table 3, benzoxazoles and benzothiazoles were also been converted from corresponding *o*-aminophenol and *o*-aminothiophenol in high yields.

Based on these results and the literature reports about the synthesis of benzimidazoles and TEMPO-catalyzed aerobic oxidative reactions previous studies,[19,25-26] a possible mechanism for the aerobic oxidative synthesis of 2-substituted benzimidazole in this system was proposed as shown in Scheme 1. First, the condensation of *o*-phenylenediamine with aldehyde takes place to form imine **1**, and then the imine further reacted with another amine group of *o*-phenylenediamine resulting in the formation of benzimidazoline **2**. The nitroxyl radical of [Imim-TEMPO][Cl] oxidized cyclo-dehydrogenation of **2** to afford the final product benzimidazole and was turned into hydroxylamine ([Imim-TEMPOH][Cl]) itself. The oxidation of [Imim-TEMPOH][Cl] into [Imim-TEMPO][Cl] could proceed smoot-hly with the help of O_2.

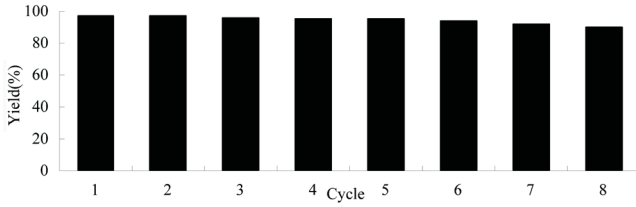
Scheme 1 A possible mechanism for synthesis of 2-arylbenzimidazoles catalyzed by [Imim-TEMPO][Cl] in [C_{12}mim]Br/*o*-xylene system



The recyclability of the catalytic system was also investtigated. After completion of the reaction, the mixture was allowed to cool to room temperature, the organic phase was separated by decantation and the residual consist of

[Imim-TEMPO][Cl] and [C_{12}mim]Br, concentrated to remove generated water and reused without further purification. Fresh substrates, solvent were heated to 120 °C for 0.5 h with stirring, then the residual [Imim-TEMPO][Cl] and [C_{12}mim]Br were recharged to the mixture to react once again. The procedure was successfully repeated for at least 8 times without great loss of catalytic activity (Scheme 2). The yield of the reaction was decreased obviously after 8 times of recycle.

Scheme 2 Repeating reactions using recovered [Imim-TEMPO][Cl] and [C_{12}mim]Br



CONCLUSIONS

In summary, we have developed a highly efficient, recyclable, new temperature-dependent biphasic system for the aerobic oxidative synthesis of benzimidazoles, benzoxazoles and benzothiazoles by using [Imim-TEMPO][Cl] as catalyst and molecular oxygen as oxidant in [C_{12}mim]Br/*o*-xylene media. The method overcomes the earlier disadvantages like the recycle of TEMPO, waste generation and the use of additives. This catalytic oxidation method has an environmentally friendly feature and provides an attractive method to synthesize benzmidazoles, benzoxazoles and benzothiazoles.

EXPERIMENTAL

All starting materials were purchased from commercial sources and used without further treatment. Melting points were determined on a Thomas Hoover capillary apparatus and were uncorrected. ^{1}H NMR (500 MHz) was recorded on a Bruker 500 spectrometer with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on an Agilent technologies 6110 quadrupole LC/MS equipped with an electrospray ionization (ESI) probe operating in positive ion mode. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. Yields refer to the isolated yields of the products after purification by silica-gel column chromatography (300 mesh). All starting chemicals are commercially available. [C_{12}mim]Br was prepared by the literature procedure[23]. [Imim-TEMPO][Cl] was prepared by the procedure given in the literature.[24]

Typical Procedure for synthesis of benzimidazoles: *o*-phenylenediamine (0.54 g, 5 mmol) and benzaldehyde (0.53 g, 5 mmol) were placed in a 30 mL three-necked flask containing *o*-xylene (15 mL). The reaction mixture was stirred at 120 °C for 0.5 h. [C_{12}mim]Br (0.67 g, 2 mmol) and [Imim-TEMPO][Cl] (0.0826 g, 0.25 mmol) were then added, and stirred at 120 °C under oxygen atmosphere for several hours till the starting materials were completely disappeared as determined by TLC. The organic phase was separated, and then ionic liquid phase washed with *o*-xylene and combined with the organic solvent, concentrated under vacuum and the product was purified by using silica gel column chromatography (n-hexane/EtOAc = 7:3) to afford the corresponding pure product.

REFERENCES

1. Soderlind, K.-J.; Gorodetsky, B.; Singh, A. K.; Bachur, N.; Miller, G. G.; Loun, J. W. *Anti-Cancer Drug Des.* **1999**, *14*, 19.
2. Gravalt, G. L.; Baguley, B. C.; Wilson, W. R.; Denny, W. A. *J. Med. Chem*. **1994**, *37*, 4338.
3. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
4. Kim, J. S.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVoie, E. J. *J. Med. Chem*. **1996**, *39*, 992.
5. Roth, T.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Buckheit, Jr., R. W.; Michejda, C. J. *J. Med. Chem*. **1997**, *40*, 4199.
6. Wang, Y.; Sarris, K.; Sauer, D. R.; Djuric, S. W. *Tetrahedron Lett*. **2006**, *47*, 4823.
7. a) Huang, W.; Scarborough, R. M. *Tetrahedron Lett*. **1999**, *40*, 2665; b) Chi, Y.-C.; Sun, C.-M. *Synlett* **2000**, 591; c) Kumar, D.; Jacob, M. R.; Reynolds, M. B.; Kerwin, S. M. *Bioorg. Med. Chem.* **2002**, 3997; d) Gong, B.; Hong, F.; Kohm, C.; Bonham, L.; Klein, P. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 1455; e) Huang, S.-T.; Hsei, I.-J.; Chen, C. *Bioorg. Med. Chem*. **2006**, *14*, 6106.
8. a) Dunwell, D. W.; Evans, D.; Smith, C. E.; Williamson, W. R. N. *J. Med. Chem*. **1975**, *18*, 692; b) Dzvinchuk, I. B.; Vypirailenko, A. V.; Lozinskii, M. O. *Russian. J. Org. Chem*. **1998**, *34*, 685.
9. a) Barni, E.; Savarino, P. J. *J. Heterocycl. Chem.* **1979**, *16*, 1583; b) Hendrickson, J. B.; Hussoin, M. S. *J. Org. Chem*. **1987**, *52*, 4137; c) Gungor, T.; Fouquet, A.; Teulon, J.-M.; Provost, D.; Cazes, M.; Cloarec, A. *J. Med. Chem*. **1992**, *35*, 4455; d) White, A. W.; Almassy, R.; Calvert, A. H.; Curtin, N. J.; Griffin, R. J.; Hostomsky, Z.; Maegley, K.; Newell, D. R.; Srinivasan, S.; Golding, B. T. *J. Med. Chem*. **2000**, *43*, 4084; e) Biasotti, B.; Dallavalle, S.; Merlini, L.; Farina, C.; Gagliardi, S.; Parini, C.; Belfiore, P. *Bioorg. Med. Chem*.

2003, *11*, 2247.
10. a) Bougrin, K.; Loupy, A.; Soufiaoui, M. *Tetrahedron* **1998**, *54*, 8055; b) Ben-Alloum, A.; Bakkas, S.; Soufiaoui, S. *Tetrahedron Lett*. **1998**, *39*, 4481; c) Reddy, G. V.; Rao, V. V. V. N. S. R.; Narsaiah, B.; Rao, P. S. *Synth. Commun*. **2002**, 2467; d) Mao, Z.; Wang, Z.; Li, J.; Song, X.; Luo, Y. *Synth. Commun*. **2010**, *40*, 1963.
11. Stephens, F. F.; Bower, J. D. *J. Chem. Soc.* **1949**, 2971.
12. Lombardy, R. L.; Tanious, F. A.; Ramachandran, K.; Tidwell, R. R.; Wilson, W. D. *J. Med. Chem*. **1996**, *39*, 1452.
13. Bahrami, K.; Khodaei, M. M.; Nejati, A. *Green Chem*. **2010**, *12*, 1237.
14. a) Vanden Eynde, J. J.; Delfosse, F.; Lor, P.; Van Haverbeke, Y. *Tetrahedron* **1995**, *51*, 5813; b) Lee, K. J.; Janda, K. D. *Can. J. Chem*. **2001**, *79*, 1556.
15. Bhatnagar, I.; George, M. V. *Tetrahedron* **1968**, *24*, 1293.
16. Beaulieu, P. L.; Hache, B.; von Moos, E. *Synthesis* **2003**, *11*, 1683.
17. Bahrami, K.; Khodaei, M. M.; Kavianinia, J. *Synthesis* **2007**, 547.
18. Wertz, S.; Studer, A. *Green Chem*. **2013**, *15*, 3116.
19. Chen, Y.; Qian, L.; Zhang, W.; Han, B. *Angew. Chem. Int. Ed*. **2008**, *47*, 9330.
20. Karimi, B.; Biglari, A.; Clark, J. H.; Budarin, V. *Angew. Chem. Int. Ed*. **2007**, *46*, 7210.
21. Fey, T.; Fischer, H.; Bachman, S.; Albert, K.; Bolm, C. *J. Org. Chem*. **2001**, *66*, 8154.
22. Gheorghe, A.; Matsuno, A.; Reiser, O. *Adv. Synth. Catal*. **2006**, *348*, 1016.
23. Kakibe, T.; Ohno, H. *J. Mater. Chem*, **2009**, *19*, 4906.
24. Miao, C.; Wang, J. *Chem. Commun.* **2011**, *47*, 2, 2697.
25. Han, B.; Wang, C.; Han, R.; Yu, W. *Chem. Commun*. **2011**, *47*, 7818.
26. Zhu, C.; Wei, Y. *ChemSusChem* **2011**, *4*, 1082.

