Communication

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Efficient Aerobic Oxidative Synthesis of Benzimidazoles with Fe(III) based PEG_{1000} Dicationic Imidazolium Ionic Liquid/toluene Temperature-dependent Biphasic System

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A green protocol for the synthesis of benzimidazoles with Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid ($[PEG_{1000}mim_2][FeCl_4]_2$)/toluene temperature-dependent biphasic system was described. Conformed by IR analysis, $FeCl_4^-$ is the dominating anion species. It could be seen that aldehydes arylamines and aromatic aldehydes bearing electron-deficient group (-Cl,-Br,-NO_2) and electron-rich groups(-OH, -$N(CH_3)_2$) on the aromatic rings gave good yields (78-96%). Moreover, the Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid could be recycled and reused without significant loss of catalytic activity after seven runs.

Keywords: Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid; Temperature-dependent biphasic system; Benzimidazoles.

INTRODUCTION

Benzimidazoles are very useful compounds in the development of pharmaceutical industry, which exhibits significant biological activity against several viruses[1] such as HIV, HSV-1, influenza, and human cytomegalovirus (HCMV). In addition, benzimidazoles are very important intermediates in organic synthesis. Although many methods have been reported for benzimidazole synthesis, there are two general methods for the synthesis of benzimidazoles. One is the condensation of carboxylic compounds or derivative (nitrile, imidate, orthoester) with *o*-phenylenediamines, which is usually performed under strong acidic conditions, high temperatures, or microwave irradiation. The other is the oxidative dehydrogenation of schiff bases, which is often generated from the condensation of diamine and aldehydes. Various oxidants[2] such as DDQ, $FeCl_3$, MnO_2, H_2O_2, $Pb(OAc)_4$, Oxone, $PhI(OAc)_2$, and $Na_2S_2O_5K_4[Fe(CN)_6]$ have been employed in the reaction. These methods are effective, however, in view of the importance of green chemistry, the isolation of the products and the recovery of catalysts hinder the development of these systems. Therefore, developing a recyclable oxidative system would be promising from catalytic efficiency and sustainable development, exhibiting very appealing prospects in view of green chemistry.

Room temperature ionic liquids (RTILS), usually as a safe and environmentally benign solvent, has drawn increasing attention over the last decades due to its excellent advantages such as negligible volatility, thermal stability, remarkable solubility and a variety of available structures.[3] Notably, functionalized ILs containing transition metals for specific-task have attracted many researches in the synthesis and application field. In particular, Fe(III) based ILs,[4] which combines the attractive properties of both magnetic ionic liquid and lewis acid, has been reported as a successful and reusable catalyst in many organic reactions such as hydroxymethylation[5] and Friedel-Crafts reaction[6] due to its non-pollutant feature from a standpoint of sustainable chemistry and extraordinary durability for air prior to other transition metals.

Besides, ionic liquids have also been designed for bearing long alkyl chain affording properties of temperature-dependent phase behavior.[7] Recently, Zhi and Hu[8] have described a new class of polyethylene glycol based dicationic ionic liquid (PEG_{1000} DIL), which exhibits a temperature-dependent phase behavior with some organic solvents (toluene or methylcyclohexane) and promotes reaction efficiently. The polyethylene glycol based dicationic ionic liquid shows good compatibility of the tandem catalyst/substrate and the ideal green catalytic process of "one-phase catalysis and two-phase separation" was achieved because the reactants were miscible with the PEG based

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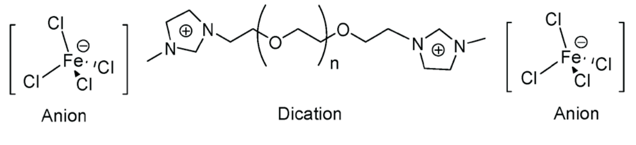
ILs at the experimental conditions, while the miscibility of the products and the PEG based ILs was extremely poor when cooled to room temperature.

As part of our continuous efforts to search for environmentally benign protocols for transition metal catalytic transformations, hererin, we report an efficient method for synthesis of benzimidazoles from aryldiamines with aromatic aldehydes catalyzed by Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid ($[PEG_{1000}mim_2][FeCl_4]_2$), which assembles the attractive properties of temperature-dependent phase behavior and Fe(III) based ILs. It was delighted to learn that the catalytic system in this paper could afford high catalytic activity and excellent durability. Moreover, the Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid could be successfully recovered by magnet force and be reused without significant loss of catalytic activity. The protocol presented here provides an efficacious strategy to achieve both high efficiency and catalysts recycling from a viewpoint of green chemistry.

RESULTS AND DISCUSSSION

The Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid are comprised of PEG_{1000} supported diimidazolium cation and anions $FeCl_4^-$ as depicted in Scheme 1. This ionic liquid was easily prepared from commercially available $FeCl_3$ and PEG supported imidazolium salt. The literature results indicated that $FeCl_4^-$ is the dominating anion species.[9]

Scheme 1 Fe(III)-based PEG_{1000} diimidazolium cation Ils



To test this kind of metal-containing lewis acidic ILs, acetonitrile was used as a basic probe molecule (Lewis base) to determine the acidity of the iron-containing ILs based on the reported principles. As can be seen in Fig. 1, acetonitrile itself shows two characteristic C-N stretching vibrations at 2252 and 2292 cm^{-1} (Fig. 1a). When acetonitrile was mixed with the iron-containing IL, a third band appeared at around 2354 cm^{-1} (Fig. 1c), indicating Lewis acid-base interactions between the iron-containing ILs and acetonitrile.

To investigate the catalytic system, we commenced the experiments for the synthesis of 2-phenyl benzimidazole, which was selected as a representative example, with *o*-phenylenediamines and benzaldehyde as model substrates. As expected, the desired target product was obtained with lower yield when only Fe(III) or PEG_{1000} dicationic imidazolium ionic liquid was used for the reaction (Table1, entry 1-2). When Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid ($[PEG_{1000}mim_2][FeCl_4]_2$) were employed to catalyze the reaction, to our delight, it was clear that the catalytic system performed well to give the desired product up to yield 96%. Also, a modest catalyst amount of 5 mol% $[PEG_{1000}mim_2][FeCl_4]_2$ (10 mol% $FeCl_3$) provided the best results of the reaction in terms of reaction yield and economy of catalyst charge (Table 1, entries 3-5). Further experiments showed that the iron with chloride is critical to the reaction which proved to be superior to nitrate and sulfate (Table 1, entries 6-7). The control experiments showed that 80 °C is appropriate in consideration of the reaction yield and catalytic activity of $[PEG_{1000}mim_2][FeCl_4]_2$ (Table 1, entries 8-11). To investigate the efficiency of the catalytic system, some commercial organic solvents was then used as the reaction media (Table 1, entry 2 and entries 12-15). As expected, the best transformation was observed in Fe(III) based PEG_{1000} dicationic ionic, revealing this ionic liquid played an important role in the reaction process with the significant catalytic performance for promotion of reaction. Also, the product and Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid was easily separated after reaction due to the

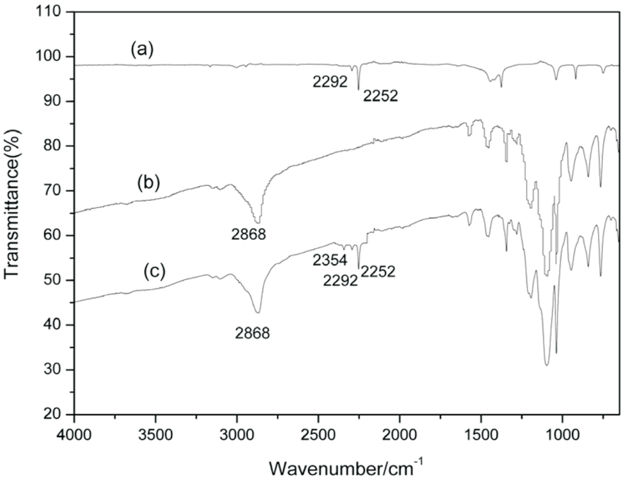


Fig. 1. IR spectra (a) acetonitrile; (b) Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid; (c) mixtures of acetonitrile and Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid.

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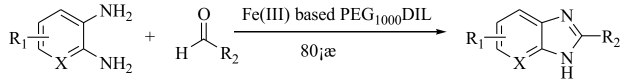
Table 1. Influence of reaction conditions on the synthesis of 2-phenyl benzimidazoles[a]

Entry	Fe(III) salts (mol%)	Solvents	Temprature (°C)	Yeild[b] (%)
1	–	biphasic system	80	45
2	$FeCl_3$ (5)	toluene	80	62
3	$FeCl_3$ (5)	biphasic system	80	76
4	$FeCl_3$ (10)	biphasic system	80	96
5	$FeCl_3$ (20)	biphasic system	80	93
6	$FeCl_3$ (40)	biphasic system	80	90
7	$Fe(SO_4)_3$ (10)	biphasic system	80	80
8	$Fe(NO_3)_3$ (10)	biphasic system	80	82
9	$FeCl_3$ (10)	biphasic system	rt	38
10	$FeCl_3$ (10)	biphasic system	40	52
11	$FeCl_3$ (10)	biphasic system	60	65
12	$FeCl_3$ (10)	biphasic system	100	79
13	$FeCl_3$ (10)	Ethanol	reflux	75
14	$FeCl_3$ (10)	DMF	80	84
15	$FeCl_3$ (10)	DMSO	80	80
16	$FeCl_3$ (10)	CH_3CN	80	85

Reaction conditions: [a] *o*-phenylenediamines 1.08 g (10 mmol) and benzaldehyde 1.06 g (10 mmol), $[PEG_{1000}mim_2][FeCl_4]_2$ (0.5 mmol), toluene (4 mL), 80 °C. [b]Yield of isolated product.

Table 2. Synthesis of benzimidazoles from aldehydes and diamines [a]



Entry	X	R_1	R_2	Time (h)	Yields[b] (%)
1	H	H	Ph	7	96
2	H	H	$4\text{-}OHC_6H_4$	9	86
3	H	H	$4\text{-}Me_2NC_6H_4$	10	80
4	H	H	$2\text{-}ClC_6H_4$	6	91
5	H	H	$4\text{-}ClC_6H_4$	4.5	95
6	H	H	$4\text{-}BrC_6H_4$	5	93
7	H	H	$2, 4\text{-}ClC_6H_3$	4	96
8	H	H	$3\text{-}NO_2C_6H_4$	5	94
9	H	$4\text{-}NO_2$	Ph	10	84
10	H	H	H[c]	8	85
11	N	H	H	10	78

Reaction conditions: [a] *o*-phenylenediamines 1.08 g (10 mmol) and aldehyde1.06 g (10 mmol), $[PEG_{1000}mim_2][FeCl_4]_2$ (0.5 mmol), toluene (4 ml), 80 °C. [b] Products were purified by silica gel column chromatography and confirmed by HPLC, ^{1}H NMR, Elemental analysis and melting point.

unique property "one-phase at high temperature and two-phase at low temperature".

After establishing previous optimal conditions, we continued to study the scope of the reaction with a series of structurally variable arylamines and aromatic aldehydes. In most cases, *o*-phenylenediamine reacted with various benzaldehyde smoothly to give the corresponding products. It could be seen that aldehydes bearing electron-deficient group (-Cl, -Br, $-NO_2$) on the aromatic rings gave higher yields of products than those bearing electron-rich groups (-OH, $-N(CH_3)_2$) (Table 2, entries 2-8). Moreover, the reason why aromatic aldehydes acted faster with *o*-phenylenediamine than aliphatic aldehydes was probably due to the conjugated effect of phenyl group of benzaldehyde (Table 2, entry 1 and entry 10). On the other hand, diamine bearing electron-deficient group on the aromatic rings (4-nitro-*o*-phenylenediamine) or containing heterocycle (2,3-diaminopyridine) proceeded more inefficiently than *o*-phenylenediamine in term of longer reaction time and lower yeild (Table 2, entry 1, entry 9 and entry 11).

The reuse of Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid was investigated by using *o*-phenylenediamine and benzaldehyde as a model reaction. The product could be simply separated by decantation from the reaction mixture while the ionic liquid phase was then subjected to a subsequent run of the reaction by charging fresh substrate. In a test of seven cycles, the Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid could be reused without significant loss of catalytic activity (Fig. 2).

The mechanism for the synthesis of benzimidazoles from aromatic diamines and aldehydes was shown in Scheme 2. The first step was dehydrated to form a schiff base. During the next step, ring closure leaded to a five-member ring and dehydrogenated with molecular oxygen

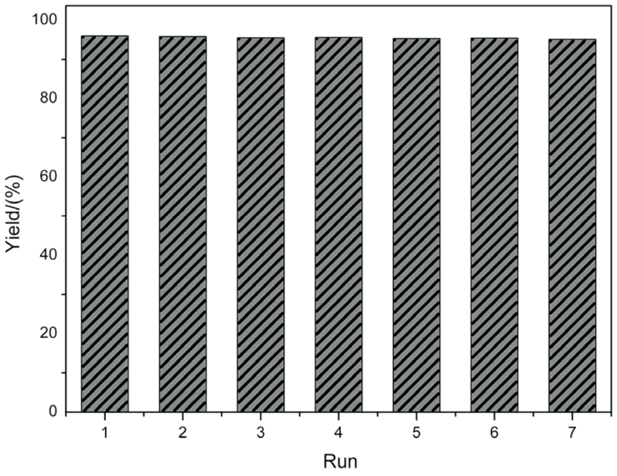


Fig. 2. Cycling reaction of Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid.

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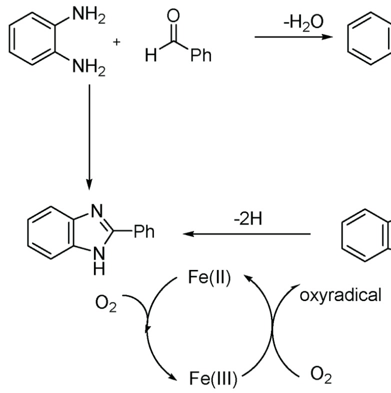
Scheme 2 The mechanism for synthesis of benzimidazole



activated by Fe(III) to form benzimidazole and the reduced Fe(II) then regenerated via two one-electron of redox cycle steps with O_2.[2,10]

CONCLUSIONS

We have developed a green and efficient method for the synthesis of benzimidazole catalyzed by Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid with excellent yields. Owing to its high efficiency and good compatibility of Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid, the catalytic system had a good catalytic performance to promote reaction effectively. Moreover, it could be recycled and reused without significant loss of catalytic activity after seven runs. This environmentally catalytic system would find a wider application in various reactions, which is an ongoing project.

EXPERIMENTAL

o-Phenylenediamines 1.08 g (10 mmol) and benaldehyde 1.06 g (10 mmol) were thoroughly mixed in Fe(III) based PEG_{1000} dicationic imidazolium ionic liquid/toluene (5 mL), the reaction mixture was stirred at 80 °C and monitorted by TLC. After completion of the reaction, the reaction mixture was extracted with ether, dried by anhydrous sodium sulfate and rotary evaporated, the residue was purified by silica gel chromatography (n-hexane: EtOAc = 10:1) gave the 2-phenyl benzimidazole (96% yield) with spectral data consistent with the assigned structures for the products. The next run was performed under identical reaction conditions.

2-Phenyl-1H-Benzimidazole: White solid; mp 293~294 °C (from Ethanol) (lit,[1] 292~293 °C); Chroatography (n-hexane: ethyl acetate = 10:1); ^1H NMR δ_H (500 MHz, DMSO-d_6): 12.93 (s, 1H, N-H), 8.19-8.18 (d, 2H, Ar-H), 7.67 (s, 1H, Ar-H), 7.56-7.54 (m, 4H, Ar-H), 7.21-7.20 (s, 2H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): d = 38.99, 39.16, 39.32, 39.49, 39.65, 39.82, 39.99, 111.35, 122.48, 126.43, 128.97, 129.86, 130.15, 151.22; MS (ESI): *m/z* = 193 $[M-1^+]$ 195 $[M+1^+]$; Elemental analysis % Calcd for $C_{13}H_{10}N_2$: C 80.41; H 5.16; N 14.43. Found: C 80.46; H 5.12; N 14.42.

REFERENCES

1. a) Porcari, A. R.; Devivar, R. V.; Kucera, L. S.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1998**, *41*, 1252. b) Migawa, M. T.; Girardet, J. L.; Walker, J. A.; Koszalka, G. W.; Chamberlain, S D.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1998**, *41*, 1242. c) Tamm, I. *Science* **1957**, *126*, 1235.
2. a) Lee, K. J.; Janda, K. D. *Can. J. Chem.* **2001**, *79*, 1556. b) Singh, M. P.; Sasmal, S.; Lu, W.; Chatterjee, M. N. *Synthesis* **2000**, 1380. c) Bhatnagar, I.; George, M. V. *Tetrahedron* **1968**, *24*, 1293. d) Bahrami, K.; Khodaei, M. M.; Naali, F. *J. Org. Chem.* **2008**, *73*, 6835. e) Stephens, F. F.; Bower, J. D. *J. Chem. Soc.* **1949**, 2971. f) Beaulieu, P. L.; Hache, B.; Von, M. E. *Synthesis* **2003**, 1683. g) Du, L. H.; Wang, Y. G. *Synthesis* **2007**, 675. h) Lombardy, R. L.; Tanious, F. A.; Ramachandran, K.; Tidwell, R. R.; Wilson, W. D. *J. Med. Chem.* **1996**, *39*, 1452. i) Patzold, F.; Zeuner, F.; Heyer, T. H.; Niclas, H. J. *Synth. Commun.* **1992**, *22*, 281. j) Shaikh, K. A.; Patil, V. A. *Org. Commun.* **2012**, *5*, 12.
3. a) Sheldon, R. *Chem. Commun.* **2001**, 2399-2407. b) Welton, T. *Coordin. Chem. Rev.* **2004**, *248*, 2459. c) Rogers, R. D.; Seddon, K. R. *Science* **2003**, *302*, 792. d) Wilkes, J. S. *J. Mol. Catal. A: Chem.* **2004**, *214*, 11. e) Yadav, J. S.; Reddy, B. V.; Premalatha, S. K. *Adv. Synth. Catal.* **1998**, *345*, 948.
4. a) Nguyen, M. D.; Nguyen, L. V.; Jeon, E. H.. Kim, J. H.; Cheong, M.; Kim, H. S.; Lee, J. S. *J. Catal.* **2008**, *258*, 5. b) Hayashi, S.; Hamaguchi, H. *Chem. Lett.* **2004**, *33*, 1590.
5. Bica, K.; Gaertner, P. *Eur. J. Org. Chem.* **2008**, 3453.
6. a) DeCastro, C.; Sauvage, E.; Valkenberg, M. H.; Olderich, W. F. H. *J. Catal.* **2000**, *196*, 86. b) Yoo, K.; Namboodiri, V. V.; Varma, R. S.; Smirniotis, P. G. *J. Catal.* **2004**, *222*, 511. c) Xiao, Y.; Malhotra, S. V. *J. Mol. Catal. A: Chem.* **2005**, *230*, 129. d) Valkenberg, M. H.; deCastro, C.; Olderich, W. F. H. *Appl. Catal. A.: Gen.* **2001**, *215*, 185.
7. Huddleston, J. G.; Rogers, R. D. *Chem. Commun.* **1998**, *16*, 1765.
8. a) Zhi, H. Z.; Lü, C. X.; Zhang, Q.; Luo, J. *Chem. Commun.* **2009**, 2878. b) Hu, Y. L.; Jiang, H.; Lu, M. *New. J. Chem.* **2011**, *35*, 292.
9. Iwata, K.; Okajlma, H.; Saha, S.; Hamaguchi, H. *Acc. Chem. Res.* **2007**, *40,* 1174.
10. a) Sharghi, H.; Asemani, O.; Khalifeh, R. *Synth. Commun.* **2008**, *38*, 1128. b) Eshghi, H.; Rahimizadeh, M.; Shiri, A.; Sedaghat, P. *Bull. Korean. Chem. Soc.* **2012**, *33*, 2515.

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