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Contributed Paper

Non-chloroaluminate Ionic Liquids Supported the Synthesis of Substituted Imidazoles using Microwave Irradiation

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ABSTRACT

An improved and rapid synthesis of 2,4,5-trisubstituted imidazoles using non-chloroaluminate ionic liquids as catalysts under microwave irradiation has been achieved. Different ionic liquids were screened and their efficacies in terms of acidity have been correlated with yields. High yields of the products, short reaction times and simple experimental procedure make this protocol complementary to the existing methods. The catalyst can be reused without obvious loss of the catalytic activity.

Keywords: substituted imidazoles, ionic liquid, catalyst, microwave irradiation.

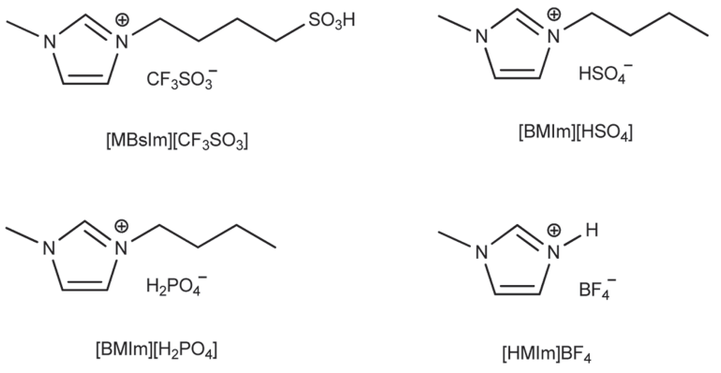
1. INTRODUCTION

The preparation of substituted imidazoles has been attracting great interest because of their applications as disinfectants, pharmaceuticals or as starting materials for these fine chemicals [1,2]. In the last decade numerous methods have been developed for the synthesis of substituted imidazoles by using various catalytic systems including DABCO [3], molecular iodine [4], silica gel/$NaHSO_4$ [5], heteropolyacids [6], HY zeolite [7], BF_3·SiO_2 [8], silica-supported Wells-Dawson acid [9], $HClO_4$-SiO_2 [10] and protic acid (such as H_3PO_4 [11], H_2SO_4 [12] and HOAc [13]). However, the search for the new readily available and green catalysts is still being actively pursued.

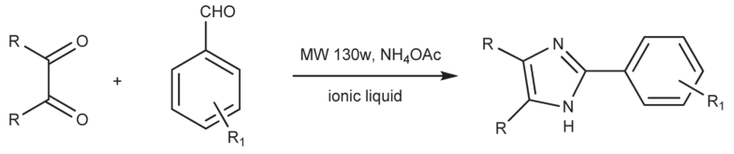
Ionic liquids have attracted extensive interest as green media in organic synthesis due to their favorable properties, for example negligible volatility and high thermal stability. Although ionic liquids were initially introduced as an alternative green reaction medium, today they have marched far beyond this border, showing their significant role in controlling the reaction as catalysts [14-17]. Recently, there were reports of the synthesis of substituted imidazoles conducted in ionic liquids such as [EMIM]OAc [18] and neutral ionic liquid[19]. Some non-chloroaluminate acidic ionic liquids, which possess the advantageous characteristics of solid acids and mineral acids, have been developed and applied for acidic reactions [20]. In continuation of our interest on the development of efficient and environmentally benign procedures using ionic liquids, we herein use non-chloroaluminate acidic ionic

liquids (scheme 1) as catalyst for the synthesis of 2,4,5-trisubstituted imidazoles in microwave irradiation.

The use of microwave irradiation has been employed for a number of organic syntheses to reduce the reaction time and rate enhancement, and to increase the selectivity and yields [21]. From the perspective of microwave chemistry, one of the key important advantages of ionic liquids is the presence of large organic positive ions with a high polarizability. Therefore, ionic liquids are very good media for absorbing microwaves, thus leading to a very high heating rate. By combining the advantages of both ILs and microwave heating, we have developed a microwave-assisted method for the fast controlled synthesis of 2,4,5-trisubstituted imidazoles using non-chloroaluminate acidic ionic liquids as catalyst (scheme 2).



Scheme 1. Structure of non-chloroaluminate acidic ionic liquids.



Scheme 2. Microwave-assisted synthesis of 2,4,5-trisubstituted imidazoles in ionic liquid.

2. MATERIALS AND METHODS

All starting chemicals (AR grade) were purchased from commercial suppliers and some chemicals were further purified by recrystallization or distillation. Melting points were determined on a Thomas Hoover capillary apparatus and were uncorrected. The IR spectra were recorded with a Bomem Michelson model 102 FTIR (ABB Bomem Inc, America). ^{1}H NMR spectra were recorded on Bruker DRX (500 MHz) spectrometer (Bruker Inc, America). Elemental analyses were performed on a Yanagimoto MT3CHN recorder (Yanagimoto Seisakusho Co., Ltd. Japan).

All used ionic liquids were prepared according to the previous methods [20].

2.1 General Procedure for Synthesis of 2, 4,5-trisubstituted Imidazoles in ILs under Microwave Heating

At room temperature, aldehyde (1mmol), benzil (1mmol) and ammonium acetate (10mmol) were added to ionic liquid (2mL). The resulted mixture was stirred completely with a glass bar and then put in the hole of the microwave reactor. The mixture was irradiated at 130W for appropriate time (checked by TLC) and the maximum temperature was 150°C (internal temperature measurement). After cooling to room temperature, ethyl acetate (2×10mL) was poured to the mixture. The extracted organic layer was washed with 10% aqueous ammonia solution, dried over anhydrous Na_2SO_4 and concentrated. The product was purified by chromatography through a column of silica-gel using ethyl acetate/petroleum ether as an eluent. The products were identified by ^{1}H NMR, IR data and physical data (mp) by comparison with literature data. The aqueous layer (containing the catalyst) was dried in a vacuum at 80°C for 2h and reused in the next run.

The spectral data for the compounds are given below:

2,4,5-Triphenyl-1*H*-imidazole (Table 3, entry 1): IR(cm^{-1}): 1216, 1638, 2470, 2993, 3434; ^{1}H NMR($CDCl_3$/DMSO-*d*6): δ 7.42-8.12(m, 15H), 12.61(brs, 1H) [22].

2-(2-Chloro-phenyl)-4,5-diphenyl-1*H*-imidazole (Table 3, entry 2): IR(cm^{-1}): 1216, 1636, 2472, 2993, 3434; ^{1}H NMR($CDCl_3$/DMSO-*d*6): δ 7.27-7.37(m, 10H), 7.45-7.49 (dd, *J*=9Hz, 1H), 7.57-7.59(d, J=8Hz, 2H), 8.02-8.05(dd, J=8.79Hz, 1H), 12.5(brs, 1H) [22].

2-(4-Bromo-phenyl)-4,5-diphenyl-1*H*-imidazole (Table 3, entry 3): IR(cm^{-1}): 1261, 1645, 2255, 2473, 3417; ^{1}H NMR($CDCl_3$/DMSO-*d*6): δ 7.25-7.48(m, 10H), 7.50-7.52(d, *J*=8Hz, 2H), 7.80-7.92(d, *J*=8.6Hz, 2H), 12.49(brs, 1H) [22].

2-(4-Nitro-phenyl)-4,5-diphenyl-1*H*-imidazole (Table 3, entry 4): IR(cm^{-1}): 845, 1443, 1522, 1540, 1602, 3056; ^{1}H NMR ($CDCl_3$/DMSO-*d*6): δ 7.25-7.57(m, 10H), 7.78(d, *J*=9Hz, 2H), 8.50(d, *J*=9Hz, 2H), 12.59(brs, 1H) [22].

2-(4-Methoxy-phenyl)-4,5-diphenyl-1*H*-imidazole (Table 3, entry 5): IR(cm^{-1}): 1216, 1636, 2465, 2893, 3428; ^{1}H NMR($CDCl_3$/DMSO-*d*6): δ 3.85(s, 3H), 6.93-6.96 (d, *J*=8.8Hz, 2H), 7.25-7.59(m, 10H), 8.02-8.05(dd, *J*=8.8Hz, 1H), 12.52(brs, 1H) [22].

2-(4,5-Diphenyl-1*H*-imidazol-2-yl)-phenol (Table 3, entry 6): IR(cm^{-1}): 1216, 1638, 2465, 2998, 3432, 3596; ^{1}H NMR($CDCl_3$/DMSO-*d*6): δ 6.87-6.95(d, *J*=7.5Hz, 2H), 6.97-7.01(d, J=8.06Hz, 2H), 7.17-7.23(m, 10H), 12.74(brs, 1H) [22].

4-(4,5-Diphenyl-1*H*-imidazol-2-yl)-phenol (Table 3, entry 7): IR(cm^{-1}): 1216, 1638, 2465, 2998, 3432, 3596; ^{1}H NMR($CDCl_3$/DMSO-*d*6): δ 6.93-6.97(d, *J*=8Hz, 2H), 7.52-7.87(m, 10H), 7.88-7.92(d, J=8.5Hz, 2H), 12.58(brs, 1H) [22].

2-Phenyl-4,5-di-*p*-tolyl-1*H*-imidazole (Table 3, entry 8): IR(cm^{-1}): 1216, 1638, 2465, 2998, 3432; ^{1}H NMR($CDCl_3$/DMSO-*d*6): δ 2.36(s, 6H), 7.14-7.34(m, 8H), 7.35-7.38(m, 5H), 12.56(brs, 1H) [22].

2-(2-Chlor-phenyl)-4,5-di-*p*-tolyl-1*H*-imidazole (Table 3, entry 9): IR(cm^{-1}): 1216, 1638, 2465, 2998, 3432; ^{1}H NMR($CDCl_3$/DMSO-*d*6): δ 2.39(s, 6H), 7.27-7.37(m, 8H), 7.45-7.49(dd, *J*=9Hz, 1H), 7.57-7.59(d, 2H), 8.02-8.05(dd, *J*=8.79Hz, 1H), 12.56(brs, 1H) [22].

2-(4-Nitro-phenyl)-4,5-di-*p*-tolyl-1*H*-imidazole (Table 3, entry 10): IR(cm^{-1}): 845, 1443, 1522, 1540, 1602, 3056; ^{1}H NMR ($CDCl_3$/DMSO-*d*6): δ 2.37(s, 6H), 7.25-7.57 (m, 8H), 7.78(d, *J*=9Hz, 2H), 8.5 (d, *J*=9Hz, 2H), 12.59(brs, 1H) [22].

2-(4-Bromo-phenyl)-4,5-di-*p*-tolyl-1*H*-

imidazole (Table 3, entry 11): IR(cm^{-1}): 1216, 1638, 2465, 2978, 3432; ^{1}H NMR($CDCl_3$/DMSO-*d*6): δ 2.35(s, 6H), 7.11-7.15(m, 4H), 7.42-7.46(m, 4H), 7.54-7.58(d, *J*=8.22Hz, 2H), 8.02-8.06(d, *J*=8.60Hz, 2H), 12.78(brs, 1H) [22].

3. RESULTS AND DISCUSSION

In the initial experiments, different non-chloroaluminate acidic ionic liquids were screened for the synthesis of 2,4,5-trisubstituted imidazoles. Herein the condensation of benzaldehyde and benzil using ammonium acetate as the ammonia source was selected to be the model. The results are summarized in Table 1. It was shown that the reactions could proceed effectively with non-chloroaluminate ionic liquids supported. In the aid of microwave irradiation, the reaction time was dramatically reduced from several hours in conventional heating to just a few minutes. In our hands, [BMIm][H_2PO_4] proved to be very active, leading to 94% yield of 2,4,5-triphenylimidazole within 4min. [HMIm]BF_4, [BMIm][HSO_4] and [MBsIm][CF_3SO_3] could also used as catalyst to promote the reaction, but their activity seems to be slightly inferior as compared with that of [BMIm][H_2PO_4]. In the absence of ionic liquids supported, the reaction proceeded sluggishly. We suggested the ionic liquids were strong promoters for the reaction.

Table 1. Conditions for synthesis of 2,4,5-triphenylimidazole in ionic liquids.

Entry	Ionic liquid	Time (h)[a]	Yield (%)[b]	Time (min)[a]	Yield (%)[b]
1	No catalyst [c]	2	10	60	14
2	[BMIm][H_2PO_4]	2	89	4	94
3	[HMIm]BF_4	2	86	4	89
4	[BMIm][HSO_4]	2	79	6	81
5	[MBsIm][CF_3SO_3]	2	77	6	79

[a] Heating in an oil bath at 100°C

[b] Isolated yield

[c] EtOH as solvent

The efficacy of the ionic liquids to promote the reaction was correlated to the Brønsted acidity of the ILs as well as the polarity of ionic liquids. A commonly used method to evaluate the acidity of a Brønsted acidity in solution is the Hammett method, wherein a basic indicator has been used to trap the dissociative proton. Yanlong Gu et al. [20] gived the Hammett function (H_0), as shown in Table 2. It indicated that ionic liquid [BMIm][H_2PO_4] exhibits a slighter Brønsted acidity than the other three non-chloroaluminate ionic liquids used in this work. Slighter Brønsted acidity may highlight the role of IL in promoting the reaction and the results were evident in Table 1.

Table 2. H_0 values of various ionic liquids.

IL	[BMIm][H_2PO_4]	[HMIm]BF_4	[BMIm][HSO_4]	[MBsIm][CF_3SO_3]
H_0	2.55	1.44	0.73	0.01

With these results in hand we decided to explore the scope of this method. The three-component coupling reactions of benzil, aldehydes and ammonium acetate in the presence of [BMIm][H_2PO_4] was conducted under microwave irradiation and the obtained

results are summarized in Table 3. It can be seen that the condensation of a series of aldehydes, benzil and ammonium acetate catalyzed by [BMIm][H_2PO_4] proceeded smoothly to give the corresponding products in high yields. Compared to the classical method, one additional important feature of the present protocol is the ability to tolerate variation in all three components simultaneously. Compare with traditional solvents and catalysts, ionic liquids are easily reused, which is superior to the conventional solvents and catalysts. When optimizing the reaction condition, the recycling performance of [BMIm][H_2PO_4] in the same model reaction was investigated. After the reaction, the products were separated from the catalytic system by extraction with ethyl acetate. The aqueous layer (containing the catalyst) was dried in a vacuum at 80°C for 2h and reused in the next run. As shown in Figure 1, the catalyst could be reused at least five times without significant decrease in catalytic activity.

Table 3. Synthesis of 2,4,5-trisubstituted imidazoles in [BMIm][H_2PO_4][a].

Entry	R	R_1	Time(min)	Yield (%)[b]
1	Phenyl	H	4	94
2	Phenyl	*o*-Cl	6	90
3	Phenyl	*p*-Br	4	96
4	Phenyl	*p*-NO_2	6	84
5	Phenyl	*o*-OH	4	91
6	Phenyl	*p*-OH	4	93
7	Phenyl	*p*-OMe	4	95
8	*p*-Tolyl	H	4	92
9	*p*-Tolyl	*o*-Cl	4	93
10	*p*-Tolyl	*p*-NO_2	6	86
11	*p*-Tolyl	*p*-Br	4	95

[a] All products were characterized by IR, ^{1}H NMR, and their mp were in comparison with that of previous literatures.

[b] Isolated yield.

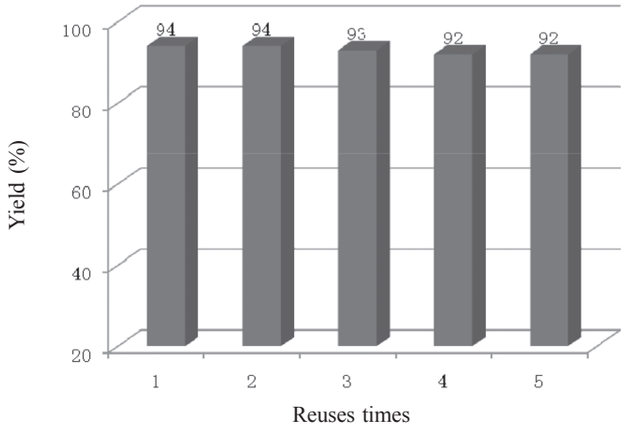


Figure 1. Reusability of [BMIm][H_2PO_4].

4. CONCLUSIONS

In conclusion, we have described an efficient protocol for the synthesis of 2,4, 5-trisubstituted imidazoles catalyzed by non-chloroaluminate ionic liquids under microwave irradiation. The use of microwave irradiation combining ionic liquid in the three-component condensation brings up the merits like high yields of the products, short reaction times, low pollution and simple experimental procedure.

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