A novel neutral ionic liquid-catalyzed solvent-free synthesis of 2,4,5-trisubstituted imidazoles under microwave irradiation

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Abstract

The three-component synthesis of 2,4,5-trisubstituted imidazoles, a typical acid-catalyzed reaction, could be conducted successfully with good to excellent yields in a neutral ionic liquid, 1-methyl-3-heptyl-imidazolium tetrafluoroborate ([HeMIM]BF$_4$), under solvent-free and microwave-assisted conditions. The combined merits of microwave irradiation and ionic liquid make the three-component condensation with safe operation, low pollution, rapid access to products and simple workup.
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1. Introduction

The structures of trisubstituted imidazoles are prevalent in natural products and pharmacologically active compounds, like the known P38 map kinase inhibitor [1] and Losartan [2]. Besides, triarylimidazoles display various bioactive effects such as herbicidal [3], fungicidal [4], analgesic [5], anti-inflammatory [6] and antithrombotic activities [7] as well. In literature, there have been many solution-phase and solid-phase condensation of benzil and aldehydes in the presence of ammonia source to generate 2,4,5-trisubstituted imidazoles [8]. In most cases, however, such reactions are carried out in AcOH or H$_2$SO$_4$ medium by refluxing for several hours. Obviously, such reaction conditions bring heavy burden to environment and equipments as well as dangerous operation. Besides, an additional acidic catalyst was indispensable for such condensation in solvent-free pattern [9].

Due to the environmental concerns, ionic liquids have attracted more and more attentions as the green reaction mediums alternative to organic solvents for their low volatility, negligible vapor pressure, reasonable thermal stability, outstanding recyclability and reusability. There are many reports that acid/base-catalyzed reactions in organic solvents can be smoothly carried out in functionalized ionic liquids containing acidic/basic counterions or cations in absence of any additional catalysts. For examples, sulfonic ionic liquids as dual solvent-catalysts in Fischer esterification, alcohol dehydrodimerization, pinacol rearrangements [10], Friedel–Crafts alkylations [11] and nitration of aromatic compounds [12]; carboxyl-functionalized ionic liquids for acetalization [13] and deoximation [14]; guanidine-based ionic liquids as bases in Henry reactions [15]; amino-functionalized ionic liquid for microwave-assisted synthesis of 4H-pyrans [16]; Brönsted ionic liquid with hydrogen sulfate counterion as the catalyst in synthesis of coumarines [17], etc. The dual role of ionic liquids as solvents and promoters will dramatically expand their potential use in scale-up and clean production of significant molecules. However, it is largely desired to conduct those acid/base-catalyzed transformations in neutral ionic liquids, therefore prolonged and complicated procedure for preparation of functionalized ionic liquids can be avoided.

Since the introduction of controlled and precise microwave reactor, microwave-assisted organic synthesis (MAOS) has had a significant impact on synthetic chemistry, especially those reactions under solvent-free circumstances with the remarkable merits of reduced reaction time, improved yields, suppressed side reactions, decreased environmental pollutions and safe operations. Therefore, a large and continuing survey has been made throughout nearly all classes of thermal reactions for improvements upon microwave heating [18]. The polar nature of ionic liquids makes them ideal for use in solvent-free microwave irradiation.

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Considering the great synthetic potentiality of microwave-induced organic reactions and catalytically active ionic liquids, we herein described the three-component synthesis of 2,4,5-trisubstituted imidazoles, a typical acid-catalyzed reaction in organic solutions, could be conducted successfully with good to excellent yields in a neutral ionic liquid, 1-methyl-3-heptyl-imidazolium tetrafluoroborate ([HeMIM]BF$_4$), under solvent-free and microwave-assisted conditions in absence of any added acid as the catalyst.

2. Experimental

2.1. General methods

All the compounds used were analytical reagents and some chemicals were further purified by recrystallization or distillation. Melting point was determined on X$_4$ micro-melting apparatus. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance DMX 400 and 100 MHz instrument using TMS as internal standard in DMSO-d_6. FT-IR spectra were recorded on a Nicolet Avatar spectrophotometer. EI-MS spectra were determined on a HP 5903 mass spectrometer with 70 eV energy. Microwave synthesis was carried out on a Sanle SPII-2 single-mode microwave reactor (Made in Nanjing, China) with infrared temperature probe and successively adjustable 0–700 W output power.

2.2. General procedure for preparation of 2,4,5-trisubstituted imidazoles 2a–n in [HeMIM]BF$_4$ under microwave heating

At room temperature, aldehyde (1 mmol), benzil (1 mmol) and NH$_4$OAc (1 g) were added to [HeMIM]BF$_4$ (2 mL). 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 135 W for appropriate time (checked by TLC). After cooling to room temperature, ethyl acetate (2 × 10 mL) was poured to the mixture. The extracted organic layer was washed with 10% aqueous ammonia solution and then dried over anhydrous Na$_2$SO$_4$. The filtrate was concentrated on a rotating evaporator to offer solid which was recrystallized from EtOH/H$_2$O (7:1).
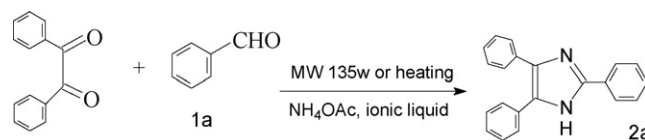
Scheme 1. Synthesis of 2,4,5-triphenylimidazole under different conditions.

Table 1
Conditions for synthesis of **2a** in ionic liquids

Entry	Ionic liquid	Time (h)[a]	Yield (%)[a]	Time (min)[b]	Yield (%)[b]
1	[HeMIM]BF$_4$	2.0	88	2.0	93
2	[BBIM]PF$_6$	3.0	86	2.5	88
3	[HeMIM]Br	3.5	78	4.0	83
4	[HMIM]Cl	4.5	71	5.5	79

[a] Heating in an oil bath at 100 °C.
[b] Heating in a microwave oven at 135 W.

2.3. General procedure for preparation of 2,2′-(1,4-phenylene)-bis(4,5-diphenyl)-1H-imidazole 4 in [HeMIM]BF$_4$ under microwave heating

At room temperature, terephthaldi-carboxyaldehyde (1 mmol), benzil (1 mmol) and NH$_4$OAc (1 g) were added to [HeMIM]BF$_4$ (2 mL). 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 135 W for 4 min (checked by TLC). After cooling to room temperature, 10% aqueous ammonia solution (20 mL) was poured in the mixture to afford a large amount of solid. The solid was filtrated and washed successively with water, ether, ethyl acetate and ethanol. After dried in vacuum at 60 °C for 2 h, pale yellow solid was obtained with enough purity for spectral analysis.

3. Results and discussion

Firstly, the condensation of benzaldehyde and benzil using NH$_4$OAc as the ammonia source was selected to be the model (Scheme 1). Four neutral imidazolium-type ionic liquids were screened as the reaction medium (Fig. 1).

Evidently, the selected four imidazolium ionic liquids were all the suitable medium for the preparation of 2,4,5-triphenylimidazole **2a** in good to excellent yields (Table 1). In the aid of microwave irradiation, the reaction time was dramati-
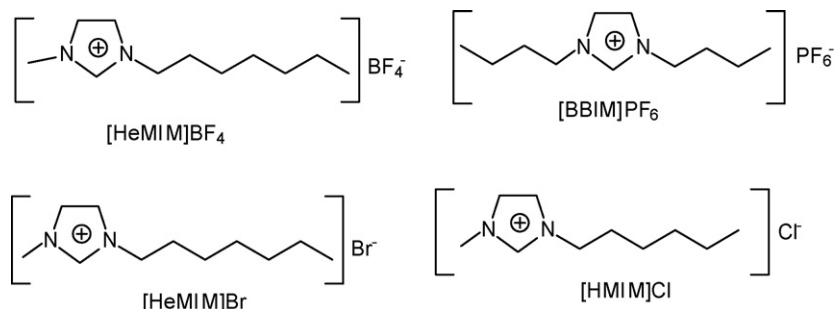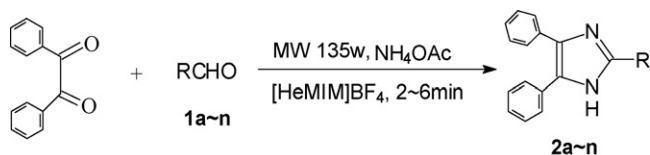

Fig. 1. Structures of four neutral ionic liquids.

Scheme 2. Microwave-assisted synthesis of 2,4,5-trisubstituted imidazoles in [HeMIM]BF$_4$.

Table 2
Results of [HeMIM]BF$_4$ catalyzed synthesis of 2,4,5-trisubstituted imidazoles

| Entry	Product	R	Time (min)	Yield (%)[a]
1	**2a**	C$_6$H$_5$	2.0	93
2	**2b**	4-FC$_6$H$_4$	2.0	93
3	**2c**	4-ClC$_6$H$_4$	2.5	91
4	**2d**	4-BrC$_6$H$_4$	3.0	87
5	**2e**	4-CF$_3$C$_6$H$_4$	3.0	86
6	**2f**	2-ClC$_6$H$_4$	5.0	82
7	**2g**	3-O$_2$NC$_6$H$_4$	3.0	96
8	**2h**	2,4-Cl$_2$C$_6$H$_4$	6.0	74
9	**2i**	Piperonyl	4.0	83
10	**2j**	4-CH$_3$C$_6$H$_4$	3.0	91
11	**2k**	4-CH$_3$OC$_6$H$_4$	2.5	93
12	**2l**	4-N,N-(CH$_3$)$_2$C$_6$H$_3$	3.0	88
13	**2m**	4-HOC$_6$H$_4$	3.5	87
14	**2n**	(CH$_3$)$_2$CH	3.5	78

[a] Isolated yield.

cally reduced from several hours in conventional heating to just a few minutes. More importantly, the three-component condensation could be successfully undergone in such imidazolium-type neutral ionic liquids in the absence of any additional acid. Due to their dual actions as solvents and catalysts, the reaction system turned clean and negligible pollution in avoidance of corrosive acid and organic solvent, while the absence of additional catalyst also made the procedure low cost and ready workup. Besides, it seemed that counterions also displayed different impact on the catalytic capability of the selected ionic liquids, therefore [HeMIM]BF$_4$ was the best candidate owning to the best yield and shortest time for the reaction in it, the following reactions were all treated with it.

According to the above result, the microwave-accelerated one-pot formations of 2,4,5-trisubstituted imidazoles in [HeMIM]BF$_4$ were extended to other aldehydes to survey the scope of such protocol (Scheme 2).

It was indicated from Table 2 that a wide range of aldehydes could be utilized as the effective candidates in the ionic liquid promoted preparation of 2,4,5-trisubstituted imidazoles **2a–n** in good to excellent yields through the solvent-free and microwave-assisted three-component condensations in one-pot pattern. There were no remarkable differences in yields and reaction time between arylaldehydes with electron-donating groups and those with electron-withdrawing groups. However, it seemed that vicinal effect from substituents on arylaldehydes existed since 2-chlorobenzaldehyde **2f** and 2,4-dichlorobenzaldehyde **2h** took prolonged reaction time to afford relatively low yields (entry 6 and 8). Besides, aliphatic aldehydes with short carbon chains like isobutyraldehyde **2n** could also be carried out the three-component condensation successfully in [HeMIM]BF$_4$ without any aid of additional catalyst. The other side, however, aliphatic aldehydes with long chains such as *n*-heptaldehyde was unable to provide the desired product in an acceptable yield, a complicated mixture with six undetermined constituents was offered after the three corresponding substrates were irradiated for 4 min. The shortened or prolonged reaction time could not further improve its reactivity.

It was unexpected that ester bond on 4-formylphenyl acrylate **2o** was so incompatible with the reaction conditions that 2-(4-hydroxy-phenyl)-4,5-diphenyl-imidazole **2m** was obtained in good yield instead (Scheme 3). The hydrolysis of ester bond was not special for [HeMIM]BF$_4$, the case was the same in the other neutral ionic liquids like [HeMIM]Br and [BBIM]PF$_6$. All of them could play the interesting roles in transformations from **2o** to **2m** within short irradiation time, except that [HeMIM]BF$_4$ displayed more capability to accomplish such transformation. It was assumed that the hydrogen source in hydrolysis might be from the air since the reaction was carried out in an open vessel.

Recently, it was reported [19] that bisimidazole derivatives of lophine displayed interesting and useful piezochromism, photochromism and themochromism properties in their solid states as well as solvatochromism, haolchromism and photochromism characteristics in solutions. The traditional method for their preparations was to reflux the mixtures of benzil, bisaldehydes and NH$_4$OAc in acetic acid for 5 h. In our case, however, benzil and terephthaldicarboxyaldehyde 3 could react smoothly with NH$_4$OAc *via* microwave heating in [HeMIM]BF$_4$ to offer 2,2′-(1,4-phenylene)-bis(4,5-diphenyl)-1*H*-imidazole **4** in 65% yield within just 4 min (Scheme 4). Similarly, the generation of

	Time(min)	Yield(%)
[HeMIM]Br	5.5	81
[HeMIM]BF$_4$	2.5	90
[BBIM]PF$_6$	3.5	86
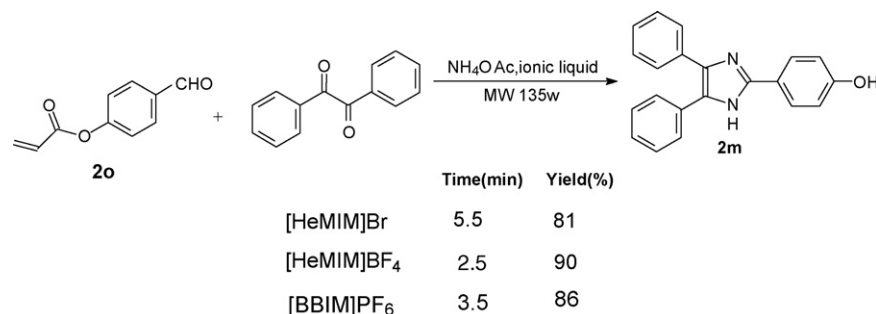
Scheme 3. Transformation of **2o** to **2m** in neutral ionic liquids.
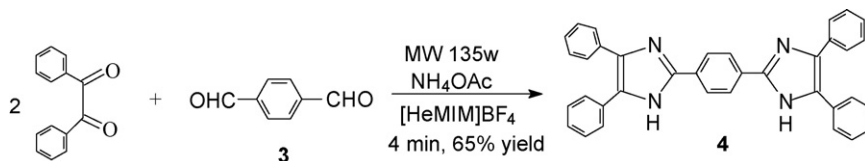
Scheme 4. [HeMIM]BF$_4$ catalyzed synthesis of compound **4**.
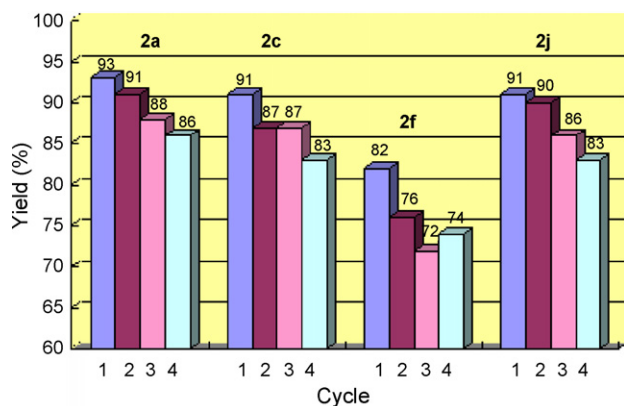
Fig. 2. Cycles of [HeMIM]BF$_4$ in synthesis of **2a**, **2c**, **2f** and **2j**.

compound **4** could also be carried out in a neutral ionic liquid without any added acid involved.

The issue for recycle and reuse which is a key index to evaluate the quality of an ionic liquid was altogether investigated on [HeMIM]BF$_4$ (Fig. 2). It was found that [HeMIM]BF$_4$ as the reaction medium could be easily isolated from the reaction mixture by extraction with ethyl acetate. The residue ionic liquid could be activated *via* heating at 70 °C for 3 h in a vacuum oven. Through this step, the opaque ionic liquid would turn transparent again with deep yellow color. Four aldehydes resulting in products **2a**, **2c**, **2f** and **2j** were selected to test the catalytic capability of the recycled ionic liquid. It was shown that [HeMIM]BF$_4$ was so extremely suitable as the catalytically active medium that the yields of the products were not dramatically decreased even after four cycles.

Acknowledgment

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2006.10.004.

References

[1] J. Boehm, J. Smietana, M. Sorenson, R. Garigipati, T. Gallagher, P. Sheldrake, J. Bradbeer, A. Badger, J. Laydon, J. Lee, L. Hillegass, D. Griswold, J. Breton, M. Chabot-Fletcher, J. Adams, J. Med. Chem. 39 (1996) 3929.
[2] G.J. Griffiths, M.B. Hauck, R. Imwinkelried, J. Kohr, C.A. Roten, G.C. Stucky, J. Org. Chem. 64 (1999) 8084 (and references therein).
[3] R. Liebl, R. Handte, H. Mildenberger, K. Bauer, H. Bieringer, Ger. Offen DE 3,604,042 (1987);
R. Liebl, R. Handte, H. Mildenberger, K. Bauer, H. Bieringer, Chem. Abstr. 108 (1987) 6018g.
[4] A.F. Pozherskii, A.T. Soldatenkov, A.R. Kareizky, Heterocycles in Life, Society, Wiley, New York, 1997, p. 179.
[5] (a) U. Ucucu, N.G. Karaburun, I. Isikdag, Farmaco 56 (2001) 285;
(b) S.E. Wolkenberg, D.D. Wisnosk, W.H. Leister, Y. Wang, Z. Zhao, C.W. Lindsley, Org. Lett. 6 (2004) 1453.
[6] J.G. Lombandine, E.H. Wiseman, J. Med. Chem. 17 (1974) 118.
[7] A.R. Phillips, H.L. White, S. Rosen, Eur. Pat. Appl. EP 58 8901 (982);
A.R. Phillips, H.L. White, S. Rosen, Chem. Abstr. 98 (1982) 53894z.
[8] (a) B. Krieg, G.I. Manecke, Naturforsch 22b (1967) 132;
(b) J.G. Lombardino, E.H. Wiseman, J. Med. Chem. 17 (1974) 1182;
(c) D.M. White, J. Sonnenberg, J. Org. Chem. 29 (1964) 1926;
(d) S. Sarshar, D. Siev, A.M.M. Mjalli, Tetrahedron Lett. 37 (1996) 835;
(e) D. Davidson, M. Weiss, M. Jelling, J. Org. Chem. 2 (1937) 319.
[9] A.Y. Usyatinsky, Y.L. Khmelnitsky, Tetrahedron Lett. 41 (2000) 5031.
[10] A.C. Cole, J.L. Jensen, I. Ntai, K.L.T. Tran, K.J. Weaver, D.C. Forbes, J.H. Davis Jr., J. Am. Chem. Soc. 124 (2002) 5962.
[11] K. Qiao, C. Yokoyama, Chem. Lett. 33 (2004) 472.
[12] K. Qiao, C. Yokoyama, Chem. Lett. 33 (2004) 808.
[13] D. Li, F. Shi, J. Peng, S. Guo, Y. Deng, J. Org. Chem. 69 (2004) 3582.
[14] D. Li, F. Shi, S. Guo, Y. Deng, Tetrahedron Lett. 45 (2004) 265.
[15] T. Jiang, H. Gao, B. Han, G. Zhao, Y. Chang, W. Wu, L. Gao, G. Yang, Tetrahedron Lett. 45 (2004) 2699.
[16] Y. Peng, G.H. Song, Catal. Commun. 8 (2007) 111.
[17] V. Singh, S. Kaur, V. Sapehiyia, J. Singh, G.L. Kad, Catal. Commun. 6 (2005) 57.
[18] (a) A. Lew, P.O. Krutzik, M.E. Hart, A.R. Chamberlin, J. Comb. Chem. 4 (2002) 95;
(b) L. Perreux, A. Loupy, Tetrahedron 57 (2001) 9199;
(c) P. Lidstrom, J. Tierney, B. Wathey, J. Westman, Tetrahedron 57 (2001) 9225.
[19] N. Fridman, S. Speiser, M. Kaftory, Crystal Growth Des. 6 (2006) 1653.