Zwitterionic-Type Molten Salt-Catalyzed Multicomponent Reactions: One-Pot Synthesis of Substituted Imidazoles Under Solvent-Free Conditions

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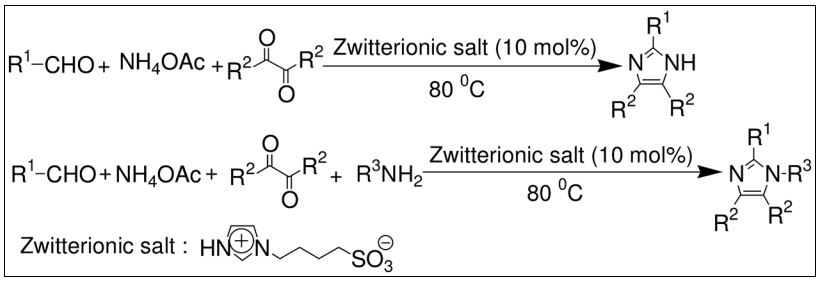
Received November 12, 2010
DOI 10.1002/jhet.924
Published online 29 October 2012 in Wiley Online Library (wileyonlinelibrary.com).



4-(1-Imidazolium) butane sulfonate is an excellent catalyst for the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles through the condensation of 1,2-dicarbonyl compounds, aldehydes, and ammonium acetate or amine *via* multicomponent condensation strategy under solvent-free conditions. The key advantages of this process are high yields, reusability of catalyst, environmental friendliness, easy work-up and purification of products by nonchromatographic methods.

J. Heterocyclic Chem., **49**, 1224 (2012).

INTRODUCTION

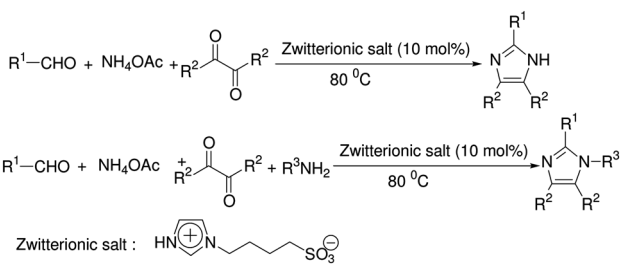
Multi-component reactions get extra attention in modern organic synthesis and medicinal chemistry because they are high atom economy and high selectivity processes [1]. One-pot catalytic conversion of organic reactions with readily available, nontoxic, and inexpensive reagents has attracted significant research interest in recent years [2]. The multisubstituted imidazoles exhibit wide ranges of biological activities such as anti-inflammatory [3], anti-allergic [4], analgesic activity [5], glucagon receptor antagonism [6], plant growth regulators [7], therapeutic agents [8], antibacterial [9], antitumour [10], and also pesticides [11], etc. There are many important drugs such as Omeprazole, Eprosartan, and Trifenagrel having functionalized imidazole motif [12]. In addition, recent development of green chemistry and organometallic chemistry expands the utility of imidazoles as ionic liquids [13]. A broad utility range has made imidazoles prime synthetic targets thereby accentuating the need to develop newer synthetic routes for imidazole derivatives.

In the last decade numerous methods have been developed for the synthesis of substituted imidazoles by using various catalytic systems. Recently L-proline and ionic liquids catalyzed transformations have been also reported [14]. Although these methods are quite useful, many of these methods suffer from one or more disadvantages such as the use of expensive moisture sensitive metallic reagents, longer reaction times, tedious separation procedures and use of large amount of toxic solvents. To avoid these limitations, the discovery of a new and efficient catalyst with high catalytic activity, reusability, short reaction time, and simple work-up for the preparation of compounds under mild and practical conditions is of great interest. In continuation of our efforts towards the development of novel methodologies under green chemical approaches using zwitterionic-type molten salt [15] herein, we report a mild, efficient and facile one-pot synthesis of substituted imidazoles derivatives by the multicomponent reaction of 1,2-diketone, amine source, and aldehyde under solvent-free conditions (Scheme 1).

RESULTS AND DISCUSSIONS

To optimize the reaction conditions, the reaction of benzaldehyde and benzil was selected as a model to examine the effects of the catalyst (0–15%) and temperature. The best result was achieved by carrying out the reaction with 1:1:2 mole ratios of benzaldehyde, benzil and ammonium acetate

Scheme 1.



in the presence of 10 mol % zwitterionic salt at 80°C for 4 h (Table 1). Higher amount of the catalyst did not improve the results to a great extent.

In a typical experimental procedure, a mixture of aldehyde (1 mmol), ammonium acetate (2 mmol) and 1,2- diketone (1 mmol) in presence of 10 mol % molten salt was heated at 80°C for a certain period of time as required to complete the reaction. A wide range of structurally diverse aldehydes underwent condensation by this reaction to provide substituted imidazoles derivatives in good yields. The results are summarized in Table 2.

As evident from the results, this procedure is uniformly effective for both aliphatic and aromatic aldehydes. The aliphatic aldehydes such as *iso*-butyraldehyde, and cyclohexanecarboxaldehyde were subjected under the reaction conditions and corresponding desired products were isolated in excellent yields. Aromatic aldehydes with both activating and deactivating groups such as Me, OMe, Cl, Br, F, and NO_2 reacted to afford the corresponding products almost equally in high yields.

To explore the applicability of this method under the present reaction conditions, we found that addition of an amine in the same reaction produced 1,2,4,5-tetrasubstituted imidazoles in moderate yields (Table 3). A wide range of structurally diverse aromatic aldehydes underwent condensation by this reaction to provide substituted imidazoles derivatives in excellent yields. As evident from the results, this procedure is uniformly effective for both electron donating and electron withdrawing substituents of aromatic aldehydes. The aromatic primary amines have been successfully subjected in this method.

One of the major advantages of this method is the isolation and purification of the products, which have been achieved by simple washing and crystallization of the crude products. We also found that α-hydroxyketone such as benzoin worked very well to get the tri- and tetrasubstituted imidazoles under the present reaction conditions (Scheme 2).

Table 1

Optimization of catalyst loading and temperature.

Entry	Catalyst (mol %)	Temperature (°C)	Time (h)	Yield (%)
1	–	Room temperature	12 h	<10
2	–	80	4 h	25
3	5	80	4 h	72
4	10	60	4 h	45
5	**10**	**80**	**4 h**	**85**
6	10	80	8 h	83
7	15	80	4 h	86
8	10	100	4 h	82

The role of the catalyst in this transformation could be an activator of the aldehydic carbonyl oxygen through hydrogen bond formation with the N H of the imidazolium moiety [16], [17].

Our attention was then turned to the possibility of recycling the catalyst from the reaction media since the recovery and reuse of the catalyst are highly preferable for a greener process. At the completion of the reaction, the reaction mixture was poured into ice cool water and stirred for few minutes. The solid product was filtered under suction. The catalyst was recovered from the aqueous layer after evaporation under reduced pressure, and reused for subsequent reactions. The recovered catalyst showed almost consistent activity for four consecutive cycles.

In summary, we have demonstrated herein that imidazole-based zwitterionic-type molten salt is an excellent catalyst for the synthesis of substituted imidazoles derivatives through a multicomponent condensation reaction under solvent-free conditions. To the best of knowledge, this is the first report on the synthesis of substituted imidazoles derivatives by zwitterionic-type molten salt. The present procedure is equally effective to aliphatic and aryl aldehydes. The nonhazardous experimental conditions, reusability of the catalyst, ease of reaction, and use of metal-free catalyst are the notable advantages of this procedure. Thus, it provides a better and more practical alternative to the existing methodologies.

EXPERIMENTAL

Melting points were determined on a glass disk with an electrical bath and are uncorrected. ^{1}HNMR and ^{13}CNMR spectra were run in DMSO-d_6 solution. IR spectra were taken as KBr plates. Elemental analyses were done by Perkin-Elmer autoanalyzer. All liquid reagents were distilled before use. The synthesis of zwitterionic-type molten salt, 4-(1-imidazolium) butane sulfonate (IBS) was carried out using a method similar to that reported [15].

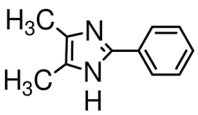
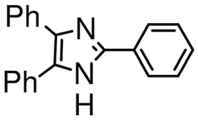
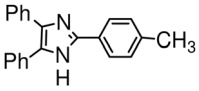
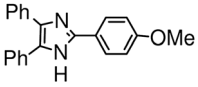
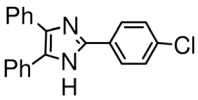
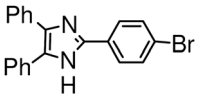
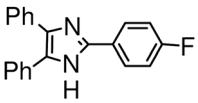
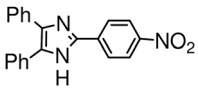
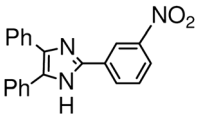
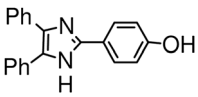
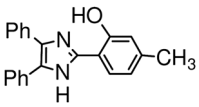
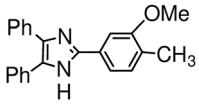
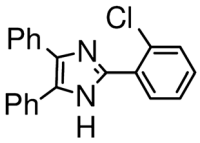
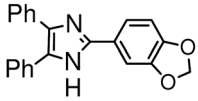
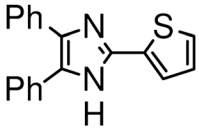
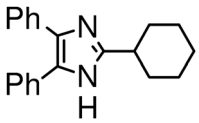
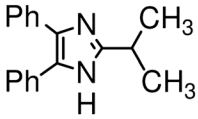
General procedure for the synthesis of 2,4,5-trisubstituted imidazoles. In a 50-mL round bottom flask 1,2-diketone (1 mmol), aldehyde (1 mmol) and ammonium acetate (2 mmol) were taken in presence of zwitterionic-salt (41 mg, 10 mol %) and the whole mixture was stirred at 80°C (oil bath) for certain period of time as required to complete the reaction. The reaction mixture, being cooled to room temperature was poured into ice cool water (10 mL) and stirred for 5–10 min. The solid product was filtered under suction, washed with ethyl acetate and then recrystallized from ethanol to obtain the pure product. The identity and purity of the product was confirmed by ^{1}H and ^{13}CNMR spectroscopic analysis. The spectral and elemental analyses of the compound which is not readily found are provided here.

The catalyst was recovered from the aqueous layer after evaporation under reduced pressure, washed with ethyl acetate to remove the organic impurities and then reused for subsequent reactions.

2-Cyclohexyl-4,5-diphenyl-1*H*-imidazole (entry 16, Table 2). White solid, mp 240–241°C; IR (KBr): 3031, 2925, 1602, 1537, 1500,

Table 2

Synthesis of 2,4,5-trisubstituted imidazoles.

Entry	Product	Time (h)	Yield[a]a (%)	Reference
1		7	65	[14]g
2		4	85	[14]a
3		4	82	[14]a
4		4.5	78	[14]a
5		4	82	[14]a
6		4.5	80	[14]b
7		4	82	[14]b
8		4.5	78	[14]a
9		5	76	[14]a
10		4.5	84	[14]a
11		4.5	72	[14]a
12		5	80	[14]c
13		4	78	[14]a
14		4	82	[14]d
15		5	80	[14]d
16		6	80	
17		5	60	[14]a

(*Continues*)

Table 2

(Continued)

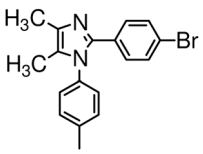
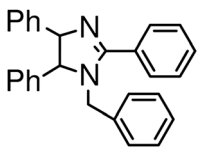
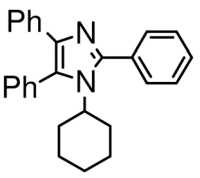
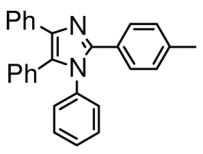
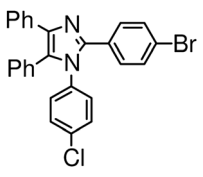
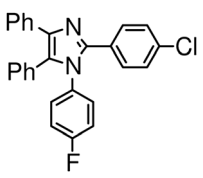
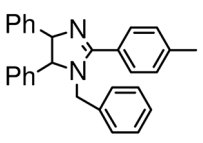
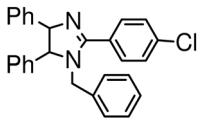
[a]Isolated yields.

1450, 1128, 912, 696 cm^{-1} ; ^{1}HNMR (400 MHz, DMSO-d_6): δ = 11.93 (s, 1H), 7.43-7.28 (m, 10H), 2.73-2.67 (m, 1H), 1.99-1.95 (m, 2H), 1.81-1.78 (m, 2H), 1.70-1.68 (m, 3H), 1.64-1.58 (m, 3H); ^{13}CNMR (100 MHz, DMSO-d_6): δ = 152.4, 135.6, 134.0, 132.2, 131.4, 129.7, 128.7, 127.8, 127.0, 126.4, 125.6, 37.2, 31.5, 25.7, 25.6; Anal. Cald for $C_{21}H_{22}N_2$: C, 83.40; H, 7.33; N, 9.26. Found: C, 83.32; H, 7.18; N, 9.21.

General procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazoles. In a 50 mL round bottom flask 1,2-diketone (1 mmol), aldehyde(1 mmol), primary amine (1 mmol) and ammonium acetate (1 mmol) were taken in presence of zwitterionic-salt (41 mg, 10 mol %) and the whole mixture was stirred at 80°C (oil bath) for 5–6 h as indicated by TLC for the completion of reaction. The reaction mixture was diluted with water and extracted with ethyl acetate. Organic layer was dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and solid product was obtained. The solid was then recrystallized from ethanol to obtain the pure product. The identity and purity of the product were confirmed by spectroscopic analysis.

Table 3

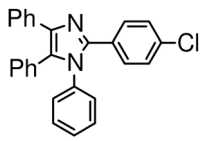
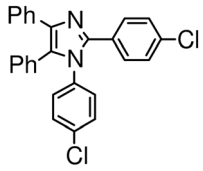
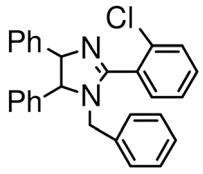
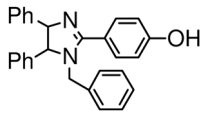
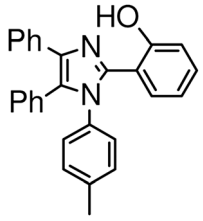
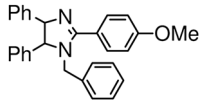
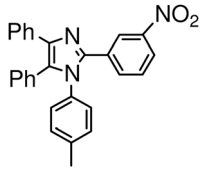
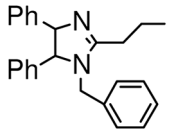
Synthesis of 1,2,4,5-tetrasubstituted tetrazoles.

Entry	Product	Time (h)	Yield[a] (%)	Reference
1		8	63	[14]g
2		5	82	[14]a
3		6	75	[14]c
4		5	78	[14]a
5		5.5	75	[14]h
6		5.5	72	[14]e
7		5	80	[14]a
8		5	78	[14]a

(*Continues*)

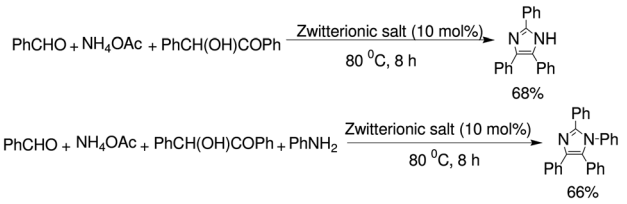
Table 3

(Continued)

Entry	Product	Time (h)	Yield[a] (%)	Reference
9		5.5	80	[14]h
10		5.5	75	[14]h
11		6	75	[14]f
12		6	78	[14]a
13		6	72	[14]e
14		5.5	76	[14]a
15		6	75	[14]e
16		6	78	[14]i

[a]Isolated yields.

Scheme 2



Acknowledgments. A.H. is pleased to acknowledge the financial support from DST (Grant No. SR/S5/GC-05/2010). A.K.B. and D.K. thank CSIR for their fellowship. A. M. acknowledges financial support from CSIR (Grant No. 01(2251)/08/EMR-II). We are thankful to DST-FIST and UGC-SAP.

REFERENCES AND NOTES

[1] (a) Zhu, J.; Bienaymé, H. Multicomponent Reactions, Eds., Wiley-VCH: Weinheim, 2005; (b) Tanaka, K.; Toda, F. Chem Rev 2000, 100, 1025; (c) Hobbs, H. R.; Thomas, N. R. Chem Rev 2007, 107, 2786; (d) Dömling, A. Chem Rev 2006, 106, 17; (e) Dömling, A.; Ugi, I. Angew Chem Int Ed 2000, 39, 3168.

[2] Mizuno, N.; Misono, M. Chem Rev 1998, 98, 199.

[3] Lambardino, J. G.; Wiesman, E. H. J Med Chem 1974, 17, 1182.

[4] Ucucu, U.; Karaburun, N. G.; Iskdag, I. Farmaco 2001, 56, 285.

[5] Chang, L. L.; Sidler, K. L.; Cascieri, M. A.; de Laszlo, S.; Koch, G.; Li, B.; MacCoss, M.; Mantlo, N.; O'Keefe, S.; Pang, M.; Rolando, A.; Hagmann, W. K. Bioorg Med Chem Lett 2001, 11, 2549.

[6] Lindberg, P.; Nordberg, P.; Alminger, T.; Brandstorm, A.; Wallmark, B. J Med Chem 1986, 29, 1327.

[7] Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, C. Z.; Lindsley, W. Org Lett 2004, 6, 1453.

[8] Heeres, J.; Backx, L. J. J.; Mostmans, J. H.; Van Cutsem, J. J Med Chem 1979, 22, 1003.

[9] Zhu, H. J.; Wang, J. S.; Patrick, K. S.; Donovan, J. L.; DeVane, C. L.; Markowitz, J. S. J.; Chromatogr, B. Anal Technol Biomed Life Sci 2007, 858, 91.

[10] Kuroda, N.; Shimoda, R.; Wada, M.; Nakashima, K. Anal Chim Acta 2000, 403, 131.

[11] Nakashima, K.; Yamasaki, H.; Kuroda, N.; Akiyama, S. Anal Chim Acta 1995, 303, 103.

[12] Chowdhury, S.; Mohan, R. S.; Scott, J. L. Tetrahedron 2007, 63, 2363.

[13] Balalaei, S.; Arabanian, A. Green Chem 2000, 2, 274.

[14] (a) Samai, S.; Nandi, G. C.; Singh, P.; Singh, M. S. Tetrahedron 2009, 65, 10155; (b) Murthy, S.N.; Madhav, B.; Nageswar, Y.V.D. Tetrahedron Lett 2010, 51, 5252; (c) Siddiqui, S. A.; Narkhede, U. C.; Palimkar, S. S.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. Tetrahedron 2005, 61, 3539; (d) Kidwai, M.; Mothsra, P.; Bansal, V.; Somvanshi, R. K.; Ethayathulla, A. S.; Dey, S.; Singh, T. P. J Mol Catal A: Chem 2007, 265, 177; (e) Nagarapu, L.; Apuri, S.; Kantevari, S. J Mol Catal A: Chem 2007, 266, 104; (f) Kantevari, S.; Vuppalapati, S. V. N.; Biradar, D. O.; Nagarapu, L. J Mol Catal A: Chem 2007, 266, 109; (g) Mukhopadhyay, C.; Tapaswi, P. K.; Drew, M. G. B. Tetrahedron Lett 2010, 51, 3944; (h) Davoodnia, A.; Heravi M. M.; Safavi-Rad, Z.; Tavakoli-Hoseini, N. Synth Commun 2010, 40, 2588; (i) Rafiee, E.; Mahdavi, H.; Joshaghani, M. Mol Div DOI: 10.1007/s11030-009-9213-1.

[15] (a) Kundu, D.; Debnath, R. K.; Majee, A.; Hajra, A. Tetrahedron Lett 2009, 50, 6998; (b) Kundu, D.; Majee, A.; Hajra, A. Catal Commun 2010, 11, 1157.

[16] Chakraborti, A. K.; Roy, S. R. J Am Chem Soc 2009, 131, 6902.

[17] Yoshizawa, M.; Hirao, M.; Ito-Akita, K.; Ohno, H. J Mater Chem 2001, 11, 1057.