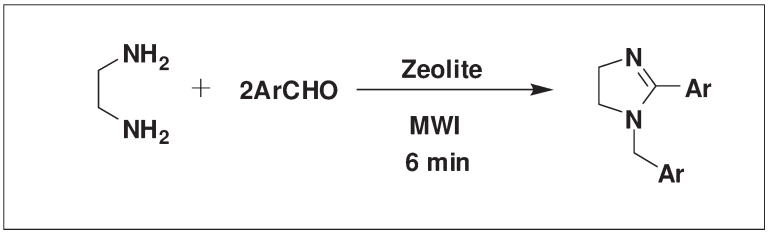
A Zeolite Promoted Expeditious One-Pot Synthesis of 1-Arylmethyl-4,5-dihydro-2-aryl-1H-imidazole

Ramakanth Pagadala,[a] Jyotsna S. Meshram,[a]* Himani N. Chopde,[a] and Nagender Reddy Panyala[b]

[a]Department of Chemistry, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur-440 033, Maharashtra, India
[b]Department of Chemistry, Faculty of Science, Masaryk University, Kotlářská 2, 611 37 Brno, Czech Republic
*E-mail: drjsmeshram@rediffmail.com

Received September 11, 2009
DOI 10.1002/jhet.314
Published online 2 March 2010 in Wiley InterScience (www.interscience.wiley.com).



A series of 1-arylmethyl-4,5-dihydro-2-aryl-1H-imidazoles were synthesized expeditiously in good yields from 1,2-diaminoethane and aromatic aldehydes in the presence of zeolite under microwave irradiation in the absence of solvent. The resulting substituted imidazoles are characterized by ^{1}H and ^{13}C NMR, elemental analysis, and mass spectral data.

J. Heterocyclic Chem., **47**, 350 (2010)

INTRODUCTION

The use of microwave (MW) irradiation as a non-conventional energy source has become of considerable interest in organic chemistry. This novel method has proved to be very efficient in various reactions, especially in organic synthesis [1–5], which has several advantages over classical thermal conditions in providing increased reaction rates, simplicity, and improved yields. The development of one-pot reaction has been of great interest in organic synthesis because this methodology provides easy access to highly complex molecules from relatively simple reagents under economically favorable reaction conditions. Thus, the combination of the one-pot strategy with the use of eco-friendly zeolite catalysts becomes a powerful means of preparation for specific target compounds to minimize pollutants and to reduce production cost [6–9]. MW irradiation has been used to effect organic reactions, such as cyclization [10], aromatic substitution [11], oxidation [12], alkylation [13], decarboxylation [14], radical reactions [15], condensation [16], peptide synthesis [17], etc.

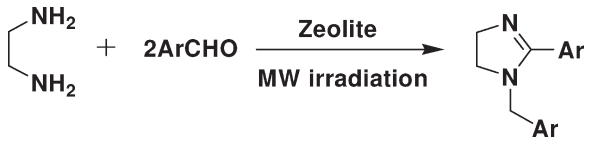
Imidazole chemistry currently attracts considerable attention, where the imidazole derivatives are extensively applied as *N*-ligands coordinating transition metals [18,19]. The application of imidazoles in medicinal chemistry [20], chemistry of natural products/alkaloids [21], and 1,3-disubstituted imidazole salts as ionic liquids [22] are well known. Several methods are reported in the literature for the synthesis of imidazoles, such as: (a) synthesis *via* hetero-Cope rearrangement [23]; (b) four-component condensation of arylglyoxals, primary amines, carboxylic acids, and iso-cyanides on Wang resin [24,25]; (c) reaction of *N*-(2-oxo)-amides with ammonium trifluoroacetate [26]. Compounds with an imidazole ring system have many pharmacological properties and play important roles in biochemical processes [27]. Organic chemists have been making extensive efforts to produce heterocyclic compounds by developing new and efficient synthetic transformations [28]. Recently, palladium and copper-catalyzed strategies have been successfully applied to the assembly of various heterocyclic compounds *via* one-pot synthesis [29].

Many of the synthetic protocols for imidazoles reported so far suffer from one or more disadvantages, such as harsh reaction conditions, poor yields, prolonged time period, use of hazardous, and often expensive acid catalysts. We have employed to achieve simple and environmentally compatible synthetic methodology for the synthesis of substituted imidazoles in the presence of zeolite under MW irradiation.

RESULTS AND DISCUSSION

Reactions were carried out simply by mixing 1,2-diaminoethane with different substituted aromatic aldehydes in the presence of zeolite under solvent-free condition

Scheme 1. MW assisted synthesis of substituted imidazoles.



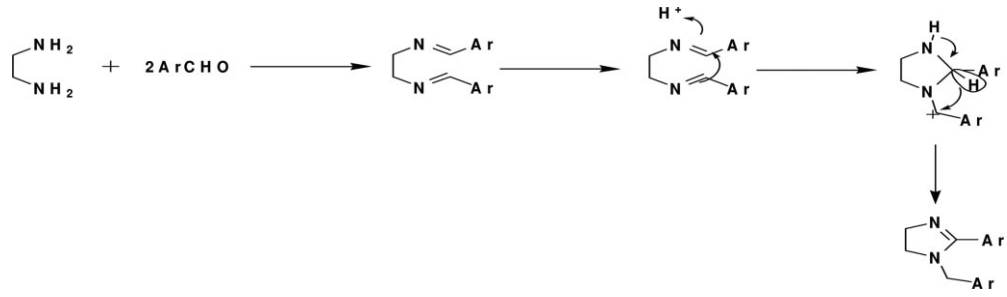
(Scheme 1). All the 1-arylmethyl-4,5-dihydro-2-aryl-1H-imidazoles derivatives were obtained in excellent yields.

This study describes a successful approach for the synthesis of substituted imidazoles using a laboratory MW reactor. This MW technology does not require linking-cleaving chemistry and afford the products immediately. In a solvent-free cyclization reaction of imidazoles is developed, which requires MW irradiation of 1,2-diaminoethane and aromatic aldehydes in the presence of zeolite. This support allows for easy separation of the solid catalyst and product by simple filtration, and in optimal conditions the supported catalyst can be reused multiple times. The readily and exclusive formation of cyclized imidazoles occurs in good yields.

The same reaction under thermal conditions (Scheme 2) affords lower yields (Table 1). Hence, it is clear from the yield comparison plot (Fig. 1) of classical and MW assisted synthesis of the substituted imidazoles that MW irradiation has been found to be easier, convenient, eco-friendly, and yield of all the products are more than good as compared with the classical method. In general, synthesis of substituted imidazole under thermal conditions may occur in two steps, formation of Schiff base and its cyclization.

The reaction may tentatively be visualized to occur *via* a tandem sequence of reactions depicted in reaction mechanism (Mechanism 1) involving (i) formation of *N*,*N*′–bis(aryl)ethylenediimine, (ii) protonation of the *N*,*N*′–bis(aryl)ethylenediimine by zeolite and ring closure leading to a five membered ring in either a sequential or a concerted manner, (iii) 1,3-hydride transfer, and (iv) deprotonation. While the aryl groups/nitrogen atom could stabilize the positively charged intermediates involved in the intermediate steps, the aromatic stabilization of the resulting imidazoles could provide the impetus for the transformation. The reaction under MW condition goes to completion in 6 min. Physical properties of the substituted imidazoles are given in Table 2.

Mechanism 1: The possible reaction mechanism.



EXPERIMENTAL

General. All the chemicals and solvents were obtained from Merck (AR grade) and were used without further purification. Melting points were taken in an open capillary tube. The MW assisted synthesis of titled compounds were carried out in a CEM – 908010, bench mate model, 300 watts laboratory MW reactor. Elemental analyses were carried out using a Perkin-Elmer, CHN elemental analyzer model 2400. ^{1}H NMR and ^{13}C NMR spectra of the imidazoles were recorded on a Bruker-Avance (300 MHz), Varian-Gemini (200 MHz) spectrophotometer using DMSO solvent and TMS as the internal standard. EI-MS spectra were determined on a LCQ ion trap mass spectrometer (Thermo Fisher, San Jose, CA, USA), equipped with an EI source.

Synthesis of 1-arylmethyl-4,5-dihydro-2-aryl-1H-imidazoles. 1,2-diaminoethane (0.108 g, 1 mmol), benzaldehyde (0.212 g, 2 mmol), and zeolite (montmorillonite K-10) (0.1 g) was thoroughly mixed. The reaction mixture was irradiated for 6 min with 100 W MWs at 110°C in MW oven in the temperature control mode. The completion of the reaction was monitored by TLC. After the irradiation was over, the reaction mixture was cooled and added into water and extracted with diethyl

Scheme 2. Synthesis of substituted imidazole under thermal condition.

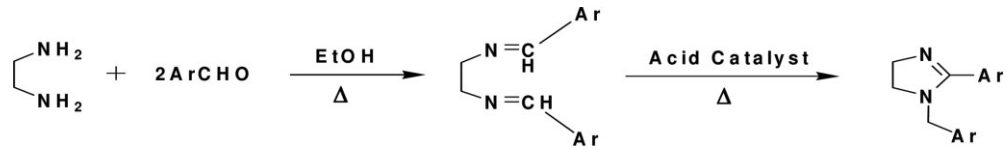


Table 1

Time and yield comparison between classical and MW irradiation.

		Microwave method		Classical method	
Compound	Formula weight	Reaction time (min)	Yield (%)[a]	Reaction time (h)	Yield (%)[a]
1	268	6	91	4	65
2	326	6	90	4	61
3	356	6	85	4	58
4	322	6	92	4	61
5	272	6	86	4	56
6	326	6	82	4	60
7	216	6	80	4	59

[a] Isolated yields

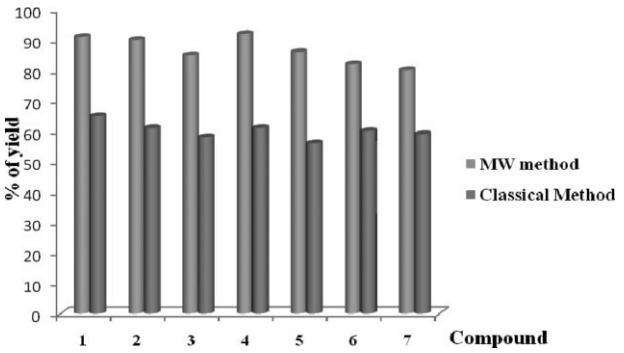


Figure 1. Graphical representation of yield comparison between classical and MW Irradiation.

ether. After filtering the zeolite particles, the ethereal layer was washed with water, dried with anhydrous sodium sulphate, and the solvent removed. The crude product was recrystallized from methanol.

Synthesis of 1-arylmethyl-4,5-dihydro-2-aryl-1H-imidazoles by classical method. A mixture of Schiff base (0.7 mmol), catalytic amount of H_2SO_4 and ethanol (50 mL) were refluxed for ~4 h. The completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was set on one side to cool. Solid deposit was collected by the filtration. The crude product was recrystallized from methanol.

1-(2-Hydroxybenzyl)-4,5-dihydro-2(2-hydroxyp henyl)-1H-imidazoles (1). ^{1}H NMR: δ 8.36 (s, 2H, —OH); 6.82–7.33 (m, 8H, Ar-CH); 4.0 (s, 2H, CH_2); 3.94 (t, J = 7.7 Hz, 2H, CH_2); 3.09 (t, J = 7.6 Hz, 2H, CH_2); ^{13}C NMR: δ 163.0, 160.8, 154.9, 131.2, 129.7, 129.2, 128.1, 122.4, 120.6, 114.3, 111.2, 50.4, 48.1, 40.9; Mass spectra, m/z = 268 (100%).

1-(3-Nitrobenzyl)-4,5-dihydro-2(3-nitrophenyl)-1H-imidazoles (2). ^{1}H NMR: δ 7.52-8.53 (m, 8H, Ar-CH); 4.04 (s, 2H, CH_2); 3.81 (t, J = 7.6 Hz, 2H, CH_2); 3.05 (t, J = 7.6 Hz, 2H, CH_2); ^{13}C NMR: δ 162.8, 147.7, 147.2, 136.2, 133.1, 132.4, 132.1, 127.9, 122.8, 122.5, 117.8, 52.3, 49.9, 49.7; Mass spectra, m/z = 326 (100%).

1-(3,4-Dimethoxybenzyl)-4,5-dihydro-2(3,4-dimethoxyphenyl)-1H-imidazoles (3). ^{1}H NMR: δ 6.39–7.02 (m, 6H, Ar-CH); 3.90 (s, 2H, CH_2); 3.69 (s, 12H, CH_3); 3.59 (t, J = 7.6 Hz, 2H, CH_2); 2.88 (t, J = 7.7 Hz, 2H, CH_2); ^{13}C NMR: δ 162.4, 150.9, 148.8, 148.5, 147.3, 129.1, 125.2, 122.0, 120.4, 114.7, 114.4, 112.1, 54.9, 50.0, 49.1, 47.9; Mass spectra, m/z = 356 (100%).

1-(4-Dimethylaminobenzyl)-4,5-dihydro-2(4-di methylaminophenyl)-1H-imidazoles (4). ^{1}H NMR: δ 7.56 (d, J = 9 and 2 Hz, 2H, Ar-CH); 7.30 (d, J = 8 and 1 Hz, 2H, Ar-CH); 6.98 (d, J = 9 Hz, 2H, Ar-CH); 6.64 (d, J = 9 Hz, 2H, Ar-CH); 3.88 (s, 2H, CH_2); 3.72 (t, J = 7.6 Hz, 2H, CH_2); 3.06 (t, J = 7.5 Hz, 2H, CH_2); 2.98 (s, 12H, CH_3); ^{13}C NMR: δ 162.7, 152.3, 152.1, 148.1, 129.9, 124.9, 112.0, 78.1, 77.5, 76.9, 62.5, 40.6; Mass spectra, m/z = 322 (100%).

1-(4-Florobenzyl)-4,5-dihydro-2(4-florophenyl)-1H-imidazoles (5). ^{1}H NMR: δ 7.64 (d, J = 8 Hz, 2H, Ar-CH); 7.24 (d, J = 8 Hz, 2H, Ar-CH); 7.09 (d, J = 9 Hz, 2H, Ar-CH); 6.98 (d, J = 9 Hz, 2H, Ar-CH); 3.86 (s, 2H, CH_2); 3.69 (t, J = 7.6 Hz, 2H, CH_2); 3.01 (t, J = 7.6 Hz, 2H, CH_2); ^{13}C NMR: δ 164.7, 162.7, 160.0, 130.9, 129.8, 128.2, 126.9, 113.8, 113.6, 50.6, 49.1, 48.2; Mass spectra, m/z = 272 (100%).

1-(2-Nitrobenzyl)-4,5-dihydro-2(2-nitrophenyl)-1H-imidazoles (6). ^{1}H NMR: δ 7.41–8.51 (m, 8H, Ar-CH); 3.97 (s, 2H, CH_2); 3.74 (t, J = 7.7 Hz, 2H, CH_2); 2.99 (t, J = 7.6 Hz, 2H, CH_2); ^{13}C NMR: δ 162.9, 147.7, 147.4, 134.2, 131.3, 128.9, 127.8, 127.0, 120.2, 50.7, 47.9, 40.1; Mass spectra, m/z = 326 (100%).

1-(Furyl)-4,5-dihydro-2(furyl)-1H-imidazoles (7). ^{1}H NMR: δ 7.84 (d, J = 2 Hz, 1H,); 7.43 (d, J = 2 Hz, 1H); 6.41–6.67 (m, 3H); 6.21 (d, J = 3 Hz, 1H); 4.59 (s, 2H, CH_2); 3.45 (t, J = 7.5 Hz, 2H, CH_2); 2.91 (t, J = 7.6 Hz, 2H, CH_2); ^{13}C NMR: δ 163.1, 147.3, 142.8, 142.1, 141.0, 109.8, 109.6, 109.2, 105.2, 45.6, 44.2, 37.8; Mass spectra, m/z = 216 (100%).

Table 2

Physical and analytical data of substituted imidazoles.

				% Calcd (Found)		
Compound	Ar	Formula	mp (°C)	C	H	N
1	*o*-OHC_6H_4	$C_{16}H_{16}N_2O_2$	90	71.62 (71.60)	6.01 (6.04)	10.44 (10.42)
2	*m*-$NO_2C_6H_4$	$C_{16}H_{14}N_4O_4$	119	58.89 (59.03)	4.32 (4.26)	17.17 (17.24)
3	*m, p*-$(OCH_3)_2C_6H_4$	$C_{20}H_{24}N_2O_4$	115	67.40 (67.62)	6.79 (6.83)	07.86 (07.81)
4	*p*-$(CH_3)_2NC_6H_4$	$C_{20}H_{26}N_4$	127	74.50 (74.31)	8.13 (8.09)	17.38 (17.30)
5	*p*-FC_6H_4	$C_{16}H_{14}N_2F_2$	97	70.58 (70.49)	5.18 (5.11)	13.95 (13.91)
6	*o*-$NO_2C_6H_4$	$C_{16}H_{14}N_4O_4$	104	58.89 (58.94)	4.32 (4.26)	17.17 (17.20)
7	2-furyl	$C_{12}H_{12}N_2O_2$	121	66.65 (66.31)	5.59 (5.70)	12.96 (12.91)

CONCLUSIONS

In this study, we reported a highly efficient MW assisted rapid and solvent-free synthesis of substituted 1H imidazoles in the presence of zeolite. MW chemistry is a green chemical method that improves reaction conditions and product yields, while reducing solvent amounts and reaction times. The one-pot nature of the present procedure makes it an acceptable alternative to multistep approaches. It also simplifies the laborious procedures and offers considerable advantages, such as: elimination of solvents, use of substances without any modification or activation, high yields, short reaction times, employment of reusable solid catalysts, and environmentally friendly character over the existing methodologies.

Acknowledgments. We greatly acknowledge to Head of the Chemistry Department RTM Nagpur University, for laboratory facilities.

REFERENCES AND NOTES

[1] Caddick, S. Tetrahedron 1995, 51, 10403.
[2] Galema, S. A. Chem Soc Rev 1997, 26, 233.
[3] Fini, A.; Breccia, A. Pure Appl Chem 1999, 71, 573.
[4] Varma, R. S. Green Chem 1999, 1, 43.
[5] Varma, R. S. J Heterocycl Chem 1999, 36, 1565.
[6] Balalaie, S.; Arabanian, A. Green Chem 2000, 2, 274.
[7] Hoelderich, W. F. Appl Catal A 2000, 487, 194.
[8] Sreekumar, R.; Padmakumar, R.; Rugmini, P. Tetrahedron Lett 1998, 39, 2695.
[9] Hoefnagel, A. J.; van Bekkum, H. Appl Catal A 1993, 87, 97.
[10] Rama Rao, A. V.; Gurjar, M. K.; Kaiwar, V. Tetrahedron: Asymmetry 1992, 3, 859.
[11] Laurent, R.; Laporterie, A.; Dubac, J.; Berlan, J. Organometallics 1994, 13, 2493.
[12] Gedye, R.; Smith, F.; Westaway, K.; Humera, A.; Baldisera, L.; Laberge, L.; Rousell, J. Tetrahedron Lett 1986, 27, 279.
[13] Yulin, J.; Yuncheng, Y. Synth Commun 1994, 24, 1045.
[14] Jones, G. B.; Chapman, B. J. J Org Chem 1993, 58, 5558.
[15] Bose, A. K.; Manhas, M. S.; Ghosh, M.; Shah, M.; Raju, V. S.; Bari, S. S.; Newaz, S. N.; Banik, B. K.; Chaudhary, A. G.; Barakat, K. J. J Org Chem 1991, 56, 6968.
[16] Villemin, D.; Martin, B. J Chem Res Synop 1994, 146.
[17] Lantos, I.; Zhang, W. Y.; Shiu, X.; Eggleston, D. S. J Org Chem 1993, 58, 7092.
[18] Kamaraj, K.; Kim, E.; Galliker, B.; Zakharov, L. N.; Rheingold, A. R.; Zuberbuhler, A. D.; Karlin, K. D. J Am Chem Soc 2003, 15, 6028.
[19] Moore L. R.; Cooks S. M.; Anderson M. S.; Schanz H.-J.; Griffin S. T.; Rogers R. D.; Kirk M. C.; Shaughnessy K. H. Organometallics 2006, 25, 5151.
[20] Wiglenda T.; Gust R. J Med Chem 2007, 50, 1475.
[21] O'Malley D. P.; Li K.; Maue M.; Zografos A. L.; Baran P. S. J Am Chem Soc 2007, 129, 4762.
[22] Kan H.-C.; Tseng M.-C.; Chu Y.-H. Tetrahedron 2007, 63, 1644.
[23] Zhang, C.; Moran, E. J.; Woiwade, T. F.; Short, K. M.; Mjalli, A. M. Tetrahedron Lett 1996, 37, 751.
[24] Sarshar, S.; Siev, D.; Mjalli, A. M. M. Tetrahedron Lett 1996, 37, 835.
[25] Claiborne, C. F.; Liverton, N. J.; Nguyen, K. T. Tetrahedron Lett 1998, 39, 8939.
[26] Yu, H. M.; Chen, S. T.; Wang, K. T. J Org Chem 1992, 57, 4781.
[27] Lambardino, J. G.; Wiseman, E. H. J Med Chem 1974, 17, 1182.
[28] Nakamura, I.; Yamamoto, Y. Chem Rev 2004, 104, 2127.
[29] (a) Dooleweerdt, K.; Ruhland, T.; Skrydstrup, T. Org Lett 2009, 11, 221. (b) Csekei, M.; Novak, Z.; Kotschy, A. Tetrahedron 2008, 64, 8992. (c) Lu, B. Z.; Zhao, W. Y.; Wei, H. X.; Dufour, M; Farina, V.; Senanayake, C. H. Org Lett 2006, 8, 3271. (d) Yao, P.-Y.; Zhang, Y.; Hsung, R. P.; Zhao, K. Org Lett., 2008, 10, 4275. (e) Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. Org Lett 2008, 10, 3535. (f) Rivero, M. R.; Buchwald, S. L. Org Lett 2007, 9, 973. (g) Yang, D.; Fu, H.; Hu, L.; Jiang, Y.; Zhao, Y. J Org Chem 2008, 73, 7841. (h) Palimkar, S. S.; Kumar, P. H.; Lahoti, R. J.; Srinivasan, K. V. Tetrahedron 2006, 62, 5109. (i) McLaughlin, M.; Palucki, M.; Davies, I. W. Org Lett 2006, 8, 3307. (j) Roesch, K.; Larock, R. C. J Org Chem 2002, 67, 86. (k) Zhu, J.; Xie, H.; Chen, Z.; Li, S.; Wu, Y. Chem Commun 2009, 2338. (l) Li, L.; Wang, M.; Zhang, X.; Jiang, Y.; Ma, D. Org Lett 2009, 11, 1309. (m) Wang, B.; Lu, B.; Jiang, Y.; Zhang, Z.; Ma, D. Org Lett 2008, 10, 2761. (n) Chen, Y.; Wang, Y.; Sun, Z.; Ma, D. Org Lett 2008, 10, 625. (o) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. Angew Chem Int Ed Engl 2009, 48, 1138. (p) Viirre, R. D.; Evindar, G.; Batey, R. A. J Org Chem 2008, 73, 3452. (q) Bossharth, E.; Desbordes, P.; Monteiro, B. N.; Balme, G. Org Lett 2003, 5, 2441. (r) Martin, R.; Cuenca, A.; Buchwald, S. L. Org Lett 2007, 9, 5521. (s) Yuan, Q.; Ma, D. J Org Chem 2008, 73, 5159. (t) Vina, D.; del Olmo, E.; Lopez-Perez, J.; Feliciano, A. S. Org Lett 2007, 9, 525.