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Efficient synthesis of Benzimidazoles using zeolite, alumina and silica gel under microwave irradiation

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Abstract

As benzimidazole ring is an important pharmacophore in modern drug discovery and benzimidazoles are very important intermediates in organic reactions, the preparation of benzimidazoles has gained considerable attention in recent years. Here, a comparative study on the synthesis of benzimidazoles from aromatic, aliphatic and heterocyclic carboxylic acid, benzonitrile and o-phenylenediamine under microwave irradiation and solvent-free conditions is catalyzed by alumina, silica gel and zeolite is presented. All the synthesized compounds are characterized by 1H-NMR, IR, Mass and CHNS analysis.

Keywords: Benzimidazole; microwave irradiation; solvent free; syntheses

1. Introduction

The benzimidazole ring is an important pharmacophore in modern drug discovery (Gilchrist 1992). Benzimidazole derivatives exhibit significant activity against several viruses such as HIV, Herpes (HSV-1) RNA influenza and human cytomegalovirus (HCMV) (Joule and Smith 1995). In addition, benzimidazoles are very important intermediates in organic reactions (Grimmett et al., 1997). Therefore, the preparation of benzimidazoles has gained considerable attention in recent years. The most important classical synthetic method for the preparation of a wide range of benzimidazoles is the condensation reaction of *o*-phenylenediamine with carboxylic acid derivatives (Grimmett et al., 1997). However, this reaction needs vigorous reaction conditions, especially when aryl carboxylic acid and hindered alkanoic acid is used. Another classical method for the preparation of benzimidazoles is the reaction between *o*-phenylenediamines and aldehydes in the presence of an acid catalyst under different reaction conditions. Whereas conversion of aldehydes to benzimidazoles is widely applicable, the work-up and purification may be laborious. Benzimidazoles have also been synthesized in solid-phase to provide a combinatorial approach. The known methods for their preparation utilize *o*-nitroanilines as intermediates or resort to direct N-alkylation of an unsubsituted benzimidazole. A number of synthetic protocols that involve *o*-nitroanilines as intermediate have evolved to include the synthesis of benzimidazoles on solid support. Recently, combination of the mineral supported and microwave irradiation has been used to carry out a wide range of reactions under solvent-free conditions. Synthesis of organic compounds under solvent free conditions, especially adapted to microwave irradiation, leads to an increase in the safety and environmental aspect. Although reports are available on the synthesis of benzimidazoles under microwave irradiation and solvent-free conditions using *o*-phenylenediamine with carboxylic acid derivatives (Saberi et al., 2009; Saberi et al., 2011; Saberi et al., 2012; Balalaie et al., 2000; Niknam et al., 2007; Mobinikhaledi et al., 2007), there are no reports on the synthesis of benzimidazoles under microwave irradiation and solvent-free conditions using *o*-phenylenediamine with Nitrile derivatives. We report only two component reactions in the presence of known and easily available solid acid catalysts such as acidic Silica gel, ϒ-Alumina and Zeolite HY). The present study involves the selective synthesis of 2-substituted benzimidazoles by three microwave assisted methods using solid acid catalyst as shown (Figs. 1 & 2; A-C). Interestingly, the microwave assisted reactions are found to be efficient, fast and high yielding in shorter time. The efficiency of the catalysts, reaction time and yields of the product obtained from microwave assisted synthesis are compared.

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2. Experimental

Chemicals and reagents

All the chemicals and solvents used for this work were obtained from Merck Ltd., and S.D. Fine Chem. Ltd., Mumbai.

Characterization

Microwave system (OM 9925-E, 230V—50Hz) Kenstar make (Korea) was used and the output of microwave power is mentioned as percent intensity *i.e.*, 20%, 40%, 60%, 100%. Melting points of the synthesized compounds were determined in open capillary tubes and were uncorrected. IR absorption spectra were recorded on Jasco FTIR-4100 series instrument, KBr diffuse reflectance, ^{1}H-NMR spectra were recorded on a Shimadzu AMX 400-Bruker 400-MHz spectrometer using DMSO-d_6 as solvent and TMS (tetramethylsilane) as an internal standard. The ^{1}H chemical shifts were reported as parts per million (ppm) downfield from TMS (Me_4Si). Mass spectra were determined in an ionization energy (EI) at 70 eV ionizing voltage. ^{1}H-NMR and IR spectra were consistent with the assigned structures. The elemental analysis (CHNS analysis) was done on a CHNS rapid analyzer. Purity of the compounds was checked by thin layer chromatography (TLC).

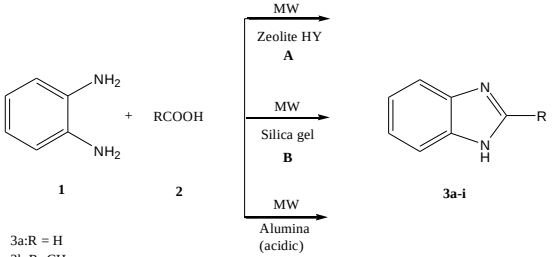
Typical procedures

General Procedure for the Synthesis of Benzimidazoles using Carboxylic acids

Synthesis of benzimidazole derivatives is outlined in Fig. 1. *o*-Phenylenediamine (216 mg, 2 mmol), Carboxylic acid derivatives (2 mmol) and 50 mg of Alumina or Silica gel or Zeolite were mixed thoroughly in a mortar. The reaction mixture was then irradiated in a domestic microwave oven for 5-9 min at 160-560 W (Table 1). The progress of reaction was monitored by TLC using n-Hexane: Ethyl acetate (90:10) as eluent. The mixture was extracted with chloroform, and the solvent was removed by rotary evaporation. Further purification by column chromatography and recrystallization gave the desired products (3a-i).

General Procedure for the Synthesis of 2-Benzimidazoles using Benzonitrile Derivatives

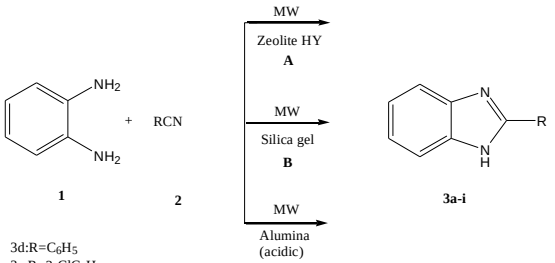
Synthesis of benzimidazole derivatives is outlined in Fig. 2. *o*-Phenylenediamine (216 mg, 2 mmol), Benzonitrile derivatives (2 mmol) and 50 mg of Alumina or Silica gel or Zeolite were mixed thoroughly in a mortar. The reaction mixture was then irradiated in a domestic microwave oven for 5-9 min at 160-560 W (Table 1). The progress of reaction was monitored by TLC using n-Hexane: Ethyl acetate (90:10) as eluent. The mixture was extracted with chloroform, and the solvent was removed by rotary evaporation. Further purification by column chromatography using n-Hexane: Ethyl acetate (80:20) as eluent and recrystallization using dichloromethane gave the desired products (3a-i).



3a:R = H
3b:R=CH_3
3c:R=CH_2Cl
3d:R=C_6H_5
3e:R=2-ClC_6H_4
3f:R=2-IC_6H_4
3g:R=2-NC_5H_4 (2-Pyridyl)
3h:R=3-IC_6H_4
3i:R=3-ClC_6H_4

MW = Microwave Irradiation

Fig. 1. Synthesis of 2-benzimidazoles under microwave irradiation and solvent-free conditions using carboxylic acid derivatives



3d:R=C_6H_5
3e:R=2-ClC_6H_4
3f:R=2-IC_6H_4
3g:R=2-NC_5H_4 (2-Pyridyl)
3h:R=3-IC_6H_4
3i:R=3-ClC_6H_4

MW = Microwave Irradiation

Fig. 2. Synthesis of 2-benzimidazoles under microwave irradiation and solvent-free conditions using benzonitrile derivatives

Products characterization data:

Benzimidazole (3a) ^{1}H-NMR (DMSO-d_6) δ: 12.5 (1H, d), 8.23 (1H, d), 7.60-7.21 (4H, m). IR (KBr) cm^{-1}: 2725, 1601, 1587, 1495, 1457, 1692, 1346, 1161. *m/z*: 118 (M^+). *Anal.* Calcd for $C_7H_6N_2$: C, 71.17; H, 5.12; N, 23.71. Found: C, 70.95; H, 5.45; N, 23.84. Melting point: 172°C.

2-Methyl-1H-benzimidazole (3b) ^{1}H-NMR (DMSO-d_6) δ: 12.2 (1H, s), 7.45-7.10 (4H, m), 2.4 (3H, s). IR (KBr) cm^{-1}: 2725, 1630, 1589, 1461, 1357, 1310, 1156. *m/z*: 133 (M^+). *Anal.* Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.71; H, 6.50; N, 20.84. Melting point: 178°C.

Table 1. The synthesis of benzimidazoles under microwave irradiation and solvent-free conditions

Compound 3(a-i)	By Carboxylic Acid Derivatives									By Benzonitrile Derivatives								
	Silica gel[a]			Alumina[b]			Zeolite HY[c]			Silica gel[a]			Alumina[b]			Zeolite HY[c]		
	Yield (%)	MW* Power (W)	Reaction time (min)	Yield (%)	MW* Power (W)	Reaction time (min)	Yield (%)	MW* Power (W)	Reaction time (min)	Yield (%)	MW* Power (W)	Reaction time (min)	Yield (%)	MW* Power (W)	Reaction time (min)	Yield (%)	MW* Power (W)	Reaction time (min)
3a	79	560	6	98	160	9	85	560	5	-	-	-	-	-	-	-	-	-
3b	73	560	6	82	160	9	74	560	5	-	-	-	-	-	-	-	-	-
3c	67	560	6	71	160	9	71	560	5	-	-	-	-	-	-	-	-	-
3d	81	560	6	85	160	9	81	560	5	88	560	6	86	160	9	75	560	5
3e	76	560	6	70	160	9	72	560	5	82	560	6	77	160	9	78	560	5
3f	80	560	6	81	160	9	74	560	5	91	560	6	81	160	9	87	560	5
3g	82	560	6	92	160	9	82	560	5	85	560	6	89	160	9	81	560	5
3h	80	560	6	81	160	9	74	560	5	80	560	6	72	160	9	86	560	5
3i	82	560	6	92	160	9	82	560	5	77	560	6	79	160	9	70	560	5

[a] Microwave assisted method using silica gel as catalyst
[b] Microwave assisted method using alumina (acidic) as catalyst
[c] Microwave assisted method using zeolite HY as catalyst
*MW=Microwave Irradiation
NOTE: all reported yields refer to isolated products

2-Chloromethyl-1H-benzimidazole (3c) ^{1}H-NMR (DMSO-d_6) δ: 12.5 (1H, s), 7.80-7.30 (4H, m), 4.25 (2H, s). IR (KBr) cm^{-1}: 2725, 1460, 1375, 1309, 1043. *m/z*: 167 (M^+), *Anal.* Calcd for $C_8H_7ClN_2$: C, 68.28; H, 3.97; N, 12.25. Found: C, 68.48; H, 3.65; N, 12.55. Melting point: 181°C.

2-Phenyl-1H-benzimidazole (3d) ^{1}HNMR (DMSO-d_6) δ: 12.9 (1H, s), 8.20-7.21 (4H, m), 7.6 (5H, m). IR (KBr) cm^{-1}: 2725, 1675, 1577, 1461, 1375, 1296, 1163, 725. *m/z*: 194 (M^+), *Anal.* Calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.10; H, 5.29; N, 14.51. Melting point: 192°C.

2-(2-Chlorophenyl)-1H-benzimidazole (3e) 1H-NMR (DMSO-d_6) δ: 13.35 (1H, s), 7.92-7.60 (4H, m), 7.59-7.20 (4H, m). IR (KBr) cm^{-1}: 2725, 1590, 1574, 1508, 1456, 1682, 1130, 1177, 760, 712. *m/z*: 228 (M^+), *Anal.* Calcd for $C_{13}H_9ClN_2$: C, 68.28; H, 3.97; N, 12.25. Found: C, 68.48; H, 3.65; N, 12.55. Melting point: 206°C.

2-(2-Iodophenyl)-1H-benzimidazole (3f) 1H-NMR (DMSO-d_6) δ: 12.8 (1H, s), 7.92-7.60 (4H, m), 7.59-7.20 (4H, m). IR (KBr) cm^{-1}: 2670, 1590, 1574, 1508, 1456, 1682, 1130, 1177, 760, 712. *m/z*: 319 (M^+), *Anal.* Calcd for $C_{13}H_9IN_2$: C, 48.77; H, 2.83; N, 8.75. Found: C, 48.23; H, 2.86; I, 39.31; N, 8.77. Melting point: 211°C.

2-(2-Pyridyl)-1H-benzimidazole (3g) 1H-NMR (DMSO-d_6) δ: 13.10(1H, s), 7.65-7.20 (4H, m), 8.70-7.70 (4H, m). IR (KBr) cm^{-1}: 2725, 1590, 1574, 1508, 1456, 1682, 1130, 1177, 732. *m/z*: 195 (M^+), *Anal.* Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.48; H, 4.21; N, 21.77. Melting point: 204°C.

2-(3-Iodophenyl)-1H-benzimidazole (3h) 1H-NMR (DMSO-d_6) δ: 12.8 (1H, s), 7.92-7.60 (4H, m), 7.59-7.20 (4H, m). IR (KBr) cm^{-1}: 2670, 1590, 1574, 1508, 1456, 1682, 1130, 1177, 760, 712. *m/z*: 319 (M^+), *Anal.* Calcd for $C_{13}H_9IN_2$: C, 48.77; H, 2.83; N, 8.75. Found: C, 48.23; H, 2.86; I, 39.31; N, 8.77. Melting point: 211°C.

2-(3-Chlorophenyl)-1H-benzimidazole (3i) 1H-NMR (DMSO-d_6) δ: 13.35 (1H, s), 7.92-7.60 (4H, m), 7.59-7.20 (4H, m). IR (KBr) cm^{-1}: 2725, 1590, 1574, 1508, 1456, 1682, 1130, 1177, 760, 712. *m/z*: 228 (M^+), *Anal.* Calcd for $C_{13}H_9ClN_2$: C, 68.28; H, 3.97; N, 12.25. Found: C, 68.48; H, 3.65; N, 12.55. Melting point: 206°C.

3. Results and discussion

Benzimidazole aryl and heteroaryl substituted derivatives were synthesized by microwave assisted methods (Figs. 1 and 2). The synthesized compounds are presented in Table 1. The structures of the synthesized compounds were confirmed by ^{1}H-NMR, IR, Mass and elemental analysis. The broad singlet peak between 12.0 to 13.5 ppm in ^{1}H-NMR spectra and –C=N- peak between 1670-1700 cm^{-1} in IR spectra confirm the structures. The reaction time for the synthesis of benzimidazole derivatives by conventional method was 180 minutes and obtained yield was 53-72%[1]. In comparison with the microwave assisted method using Silica gel as catalyst (Figs. 1 and 2; B), reaction time was 6 minutes and obtained yield was 73-91%. While for microwave assisted method using Alumina (acidic) as catalyst (Figs. 1 and 2; C), reaction time was 9 minutes and obtained yield was 70-98%. In the case of microwave assisted method using Zeolite HY as catalyst (Figs. 1 and 2; A) reaction time was 5 minutes and obtained yield was 70-87%. Thus, the reaction time reduced

several fold (approximately 96 to 98%) and the yield was increased 10 to 50%. As the reaction temperature is very important for reactant to overcome the activation energy barrier and perform the reaction, microwave has made it easy to do so. Among the three catalysts, Silica gel and Zeolite HY absorbs 70% (560 Watt) microwave irradiation intensity, while Alumina absorbs 20% (160 Watt) intensity only. Between these two methods, the synthesis of benzimidazoles using carboxylic acids and the synthesis of 2-benzimidazoles using benzonitrile derivatives, an important difference was noted; some Nitrile compounds are very toxic and are available just in gas or solution states. The workup of the reaction mixture was easy and the used catalyst was filtered and the solvent was evaporated. The catalyst could be recycled easily without significant loss of activity.

4. Conclusion

In summary, Benzimidazole aryl and heteroaryl substituted derivatives were synthesized from new microwave assisted methods. The microwave heating methods have reduced the reaction time by 10-36 times compared to conventional (180 minutes) and increase the yield nearly 10 to 50%. The catalyst could be recycled easily without significant loss of activity so that the mentioned methods are very environmentally friendly. Between these two methods, the synthesis of benzimidazoles using carboxylic acids and benzonitrile derivatives, carboxylic acids are better because of their availability and less toxicity. Among all the catalysts, γ-alumina (acidic), which has Lewis acidity is more active and beneficial, and increases the product yield (10-20%) and, reduced the microwave power (85%). γ-Alumina a Lewis acid catalyst gave excellent yields compared to other two catalysts under the reaction conditions used for the synthesis of benzimidazoles.

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