original article

JPHS

One-pot synthesis of Benzimidazole derivatives under microwave Irradiation and solvent-free condition

Ali Saberi [1 *]

1. Dept. of Chemistry, Payame Noor University, Tehran, Iran

ABSTRACT

A simple, fast, efficient and environmentally friendly method for synthesis of benzimidazole and its 2-alkyl, aryl and heteroaryl substituted derivatives was developed using zeolite HY. Two component cyclolcondensation of 1,2-phenylenediamine (o-phenylenediamine) and commercially available carboxylic acids catalyzed by zeolite HY without any solvent, under microwave irradiation led to formation of 1*H*-benzimidazole and 2-substituted derivatives in high yields and purity. The similar reaction was not applicable to the preparation of benzimidazole and its 2-alkyl, aryl and heteroaryl substituted derivatives. All the synthesized compounds were characterized by ^{1}H-NMR, IR, Mass and CHNS analysis.

Key words: Benzimidazole, zeolite HY, microwave irradiation, solvent-free

* ***Corresponding Author*** : Dr. Ali Saberi, Dept. of Chemistry, Payame Noor University, Tehran, Iran.
Tel: +98 912 3933625
e-mail: saberi121@gmail.com

1.Introduction

Benzimidazoles are very useful intermediates for development of biophamaceutical molecules. Substituted benzimidazole derivatives have found applications as diverse therapeutic agents including antiulcer, antihelmintic, antihypertensive, anticoagulant, antiallergic, analgesic, antiinflammatory, antipyretic, antibacterial, antifungal, antiviral, antiparasitic, antioxidant, anticancer and antianxiolytic (Grimmett, 1997). Because of their significant medicinal importance, the synthesis of substituted benzimidazoles has become a focus of synthetic organic chemistry. The most important classical synthetic method for preparation of a wide range of benzimidazoles is the condensation reaction of *o*-phenylenediamine with carboxylic acid or derivatives. However this reaction needs vigorous reaction conditions, especially when aryl carboxylic acid and hindered alkanoic acid is used. Several authors have reported such different vigorous conditions for the preparation of different benzimidazoles. An alternative method for the preparation of benzimidazoles is the reaction between *o*-phenylenediamines and aldehydes in the presence of an acid catalyst under various reaction conditions. Whereas conversion of aldehydes to benzimidazoles is widely applicable, the work-up and purification may be laborious (Niknam *et al*., 2007). Benzimidazoles have also been synthesized on solid-phase to provide a combinational approach. The known methods for their preparation utilize *o*-nitroanilines as intermediates or resort direct N-alkylation of an unsubsituted benzimidazole. A number of synthetic protocols that involve *o*-nitroanilines as an intermediate have evolved including the synthesis of benzimidazoles on solid support. Recently, combination of the mineral support and microwave irradiation has been used to carry out a wide range of reactions under solvent-free conditions (Mobinikhaledi *et al*., 2007). Synthesis of organic compounds under solvent-free conditions, and adopted to microwave irradiation, has lead to increased environmental and safety respect (Balalaie *et al*., 2000). Here we report a selective synthesis of benzimidazole and its 2-substituted (alkyl, aryl and heteroaryl) derivatives (3a-g) under microwave irradiation and using zeolite HY as an efficient catalyst.

2.Material and Methods

All the chemicals and solvents used for this work were obtained from E-Merck Ltd., Mumbai and S.D. Fine Chem. Ltd., Mumbai. Kenstar microwave system (OM 9925-E, 230V—50Hz) 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-d6 as solvent and TMS (tetramethylsilane) as an internal standard. The ^{1}H chemical shifts were reported in parts per million (ppm) downfield from TMS (Me4Si). 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).

2.1.General procedure

A mixture of 50 mg zeolite HY (prepared from zeolite NH4Y in an oven at 600 ^{oC} for 5 h that afforded zeolite HY), 0.5 g (4.6 mmol) of o-phenylenediamine and (9.2 mmol) of carboxylic acid was ground in a mortar until a fine powder was formed. Then the reaction mixture was transferred into an open beaker (250 ml) and irradiated with the domestic microwaves for 5 minutes with 70% power. The progress of reaction was monitored by TLC using n-Hexane: Ethyl Acetate. (90:10) as the eluent. The mixture was extracted with dichloromethane (3×30×30 cm^3), filtered, and washed with H_2O. The organic phase was removed under reduced pressure. Further purification by column chromatography (eluent n-Hexane: Ethyl Acetate. (90:10)) on silica gel yielded the desired products.

2.2.Synthesis of Benzimidazole (3a)

(0.462 g, 85%). ^{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.

2.3.Synthesis of 2-Methyl-1H-benzimidazole (3b)

(0.453 g, 74%). ^{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.

2.4.Synthesis of 2-Chloromethyl-1H-benzimidazole (3c)

(0.553 g, 71 %), ^{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 $C_8H_7C_1N_2$: C, 68.28; H, 3.97; N, 12.25. Found: C, 68.48; H, 3.65; N, 12.55.

2.5.Synthesis of 2-Phenyl-1H-benzimidazole (3d)

(0.722 g, 81%). ^{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.

2.6.Synthesis of 2-(2-Chlorophenyl)-1H-benzimidazole (3e)

(0.744 g, 72 %), ^{1}H-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 $C_{13}H_9C_1N_2$: C, 68.28; H, 3.97; N, 12.25. Found: C, 68.48; H, 3.65; N, 12.55.

2.7.Synthesis of 2-(2-Iodophenyl)-1H-benzimidazole (3f)

(1.086 g, 74 %), ^{1}H-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.

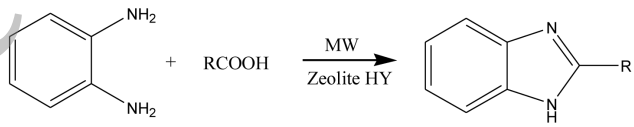
2.8.Synthesis of 2- (2-Pyridyl)-1H-benzimidazole (3g)

(0.736 g, 82 %), ^{1}H-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*9*N*3*: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.48; H, 4.21; N, 21.77.

3.Results and Discussion

Zeolites as catalysts have received considerable attention in recent years, due to their characteristic properties, such as thermal stability and acidity character. Zeolite HY has a p*Ka* of 8.2. In a classic approach, the most important synthetic method for preparing a wide range of benzimidazoles is the condensation reaction of o-phenylenediamine with carboxylic acid or derivatives (Balalaie *et al*., 2000). However this reaction needs vigorous reaction conditions to proceed, particularly when aryl carboxylic acid and hindered alkanoic acid is used. Several authors have reported such different vigorous conditions for preparation of different benzimidazoles. Other methods also need special and complex reagents. Recently, there has been a growing interest in the use of inorganic solid acids in synthesis of organic compounds (Mobinikhaledi *et al*., 2007). Solid acids, compared to liquid acids, have many advantages such as simplicity of handling and environmental protection. Among the reported solid acids, zeolites have attracted an increasing attention because of their availability, suitable acidity and thermal stability (Mobinikhaledi *et al*., 2007). The use of the zelolites also provides some advantaged such as reduced thermal degradation, better selectivity and easy work-up after reaction. Benzimidazole and its 2-alkyl, aryl and heteroaryl substituted derivatives were synthesized by microwave assisted method (Fig.1). By this method not only 2-aryl benzimidazoles but also benzimidazole, 2-alkyl benzimidazole and 2-heteroaryl benzimidazole were synthesized. The synthesized compounds are given in Tables 1. The structures of the synthesized compounds were confirmed by ^{1}H-NMR, IR, Mass and elemental analysis. The results obtained from spectroscopy also confirmed the structure of the synthesized compounds. The reaction time for the synthesis of benzimidazole derivatives through conventional method was 45 min to 4 h whereas the application of microwave reduces this time down to 5 min. the reaction time was approximately decreased by 96 to 98% and the obtained yield was increased by 10 to 50%. As heating is very important for reactant to crossover the activation barrier and perform the reaction, application of microwave provide significant advantages for the reactive progress. The workup of the reaction mixture was easy: the catalyst was filtered out and the solvent was evaporated. The catalyst could be recycled easily without significant loss of activity.

On the whole our study represents an efficient and facile method for one-pot synthesis of benzimidazole and its 2-alkyl, aryl and heteroaryl substituted derivatives with simple set-up and work-up, high yield and short reaction time that makes the method environmental friendly.



1 2(a-g) 3(a-g)

R = H, Alkyl, Aryl or Heteroaryl
MW = Microwave Irradiation

Figure 4. SDS-PAGE analysis of MES1 and MES2 expression experiments.

Table 1. Solvent-free synthesis of benzimidazoles 3(a-g) under microwave irradiation[a]

Compound	R	Yield (%)[b]
3a	H	85
3b	CH_3	74
3c	CH_2Cl	71
3d	C_6H_5	81
3e	2-ClC_6H_4	72
3f	2-IC_6H_4	74
3g	2-NC_5H_4 (2-Pyridyl)	82

[a]In all experiments, the reaction time was 5 min;
[b]all reported yields refer to isolated products

4. Acknowledgements

This study was financially supported by Payame Noor University, Asalouyeh International branch of Payame Noor University and Pars Special Economic Energy Zone.

5. References

Balalaie S, Arabanian A. One-pot synthesis of tetrasubstituted imidazoles catalyzed by zeolite HY and silica gel under microwave irradiation. *Green Chemistry*. 2000; 2:274-6.

Balalaiel S, Arabanian1 A, Hashtroudi MS, Zeolite HY. Silica Gel as New and Efficient Heterogeneous Catalysts for the Synthesis of Triarylimidazoles under Microwave Irradiation. *Monatshefte fur Chemie*. 2000; 131:945-8.

Grimmett MR. Imidazole and Benzimidazole Synthesis. *CA (San Diego): Academic Press, Inc.*, 1997.

Grimmett MR. Imidazoles and their Benzo Derivatives. In: Comprehensive Heterocyclic Chemistry. Katritzky AR, Rees CW *,eds. NY: Pergamon, vol. 5*., 1997.

Mobinikhaledi A, Zendehdel M, Hasanvand Jamshidi F. Zeolite-Catalyzed Synthesis of Substituted Benzimidazoles under Solvent-Free Condition and Microwave Irradiation. *Synthesis and Reac¬tivity in Inorganic, Metal-Organic and Nano-Metal Chemistry*. 2007; 37:175–7.

Niknam K, Fatehi-Raviz A. Synthesis of 2-Substituted Benzimidazoles and Bis-benzimidazoles by Microwave in the Presence of Alumina-Methanesulfonic Acid. *J Iran Chem. Soc.* 2007; 4:438-43.