Comparative Studies on Conventional and Microwave Assisted Synthesis of Benzimidazole and Their 2-Substituted Derivative with the Effect of Salt Form of Reactant

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Benzimidazole and their derivative were reported to have wide biological activities and were synthesized by using different solvents and ring closing agents. The present work deals with the comparative synthesis of 2-alkyl and aryl substituted benzimidazole derivative in the presence of polyphosphoric acid through microwave and conventional methods and also studied the effect of salt form of reactant for completion of the reaction. The 2-substituted aryl and alkyl benzimidazole derivative were synthesized *via* microwave and was observed to be more beneficial, in respect of yield (increases up to 10 to 50%) and time (96 to 98% was reduced) than conventional method of synthesis. This study was concluded that the salt form of reactant (*o*-phenylenediamine dihydrochloride) gave reduced colour impurities, homogenous mixing and reduced time for completion of reaction.

Key word benzimidazole; microwave assisted synthesis; conventional synthesis; *o*-phenylenediamine dihydrochloride

In the rapidly developing environment, every process needs automation to increase productivity, quality and safety with reduced manpower and time. Microwave is found to be an important tool, which fulfills these criteria.[1,2)]

In mid of 1980's, microwave irradiation was first applied towards synthetic chemistry. In 1986, first microwave-assisted synthesis paper was published by Gedye and Giguere/Majetich.[3)]

Microwave assisted organic synthesis (MAOS) is superior in many ways to traditional heating.[4—6)] The benefits of microwave assisted synthesis, including speed, increased yield and clear chemistry have provided the momentum for many chemists to switch from traditional heating method to microwave assisted chemistry. Now, microwave has become a new era in the field of synthetic chemistry.[7,8)]

Number of conventional reactions, including basic reactions and name reactions were converted into microwave-assisted synthesis such as alkylation, condensation, substitution reaction, *etc.*[9—11)] Among the reactions, cyclization reaction is a reaction resulting synthesis of various heterocyclic compounds. Through cyclization reaction, various substituted benzimidazole derivatives were synthesized in the presence of various solvents and ring closing agents such as dry benzene, xylene, *p*-tolune sulfonic acid, mercaptoacetic acid, toluene, ethanol and polyphosphoric acid (ring closing agents).[12,13)]

Benzimidazoles are five membered benzoheterocyclic compounds containing two heteroatoms. Both heteroatoms are nitrogen (N), which are present at non-adjacent position. Benzimidazoles (aryl and alkyl substituted) have wide variety of reported activities especially, antimicrobial, antitumor, antiviral, antifungal, antioxidant, antiulcer, antiamoebic, antihistaminic, anthelmintic and antihypertensive activity.[14—20)]

From 1996, various substituted benzimidazole derivatives are synthesized through microwave heating, in the presence of different solvents and catalytic agents.[21—23)]

In the present investigation, we performed a study on comparative synthesis of 2-alkyl and aryl substituted benzimidazole derivative in the presence of polyphosphoric acid (literatures reveals benzimidazole can be synthesized conventionally in the presence of ring closing agent (solvents) *e.g.* ploy phosphoric acid)[24,25)] through microwave and conventional method and studied the effect of salt form of reactant for completion of the reaction (Chart 1).

Chemistry In the conversion of conventional method to microwave assisted synthesis, the sample was started heating at minimum percentage for minimum duration, because the actual duration in which reaction will complete was not known.

Conventional synthesis of alkyl and aryl benzimidazoles was done by standard procedure.[12,13,24)] Microwave assisted synthesis of this compound was done by using the starting material as its salt form (*o*-phenylenediamine was converted into *o*-phenylenediamine dihydrochloride).

The development of method was started with addition of reagents in the dried Erlenmeyer flask and the mixture was homogenized thoroughly, the flask was capped with small funnel and the hole of funnel was plugged with cotton. The reaction mixture was kept in microwave cavity (applicator) for heating, at minimum percentage (20%) for minimum time duration (10 s). After completion of heating, reaction mixture was taken out of cavity. A TLC of the reaction mixture and the starting compound were run in suitable solvent system. Each time, the sample was taken by, removing the cotton from the hole of funnel and dipping the capillaries in a reaction mixture. After development of TLC, the progress of reaction was known. According to that the rate of heating was increased, on completion of reaction, a constant TLC spot was observed. From this, the time duration and heating percentage in which reaction got complete was observed.

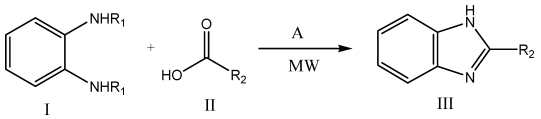

Chart 1

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Experimental

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. LG-health wave microwave system (MG-607APR, 230 V—50 Hz) 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 FT/IR-470 Plus, KBr diffuse reflectance, ^{1}H-NMR spectra were recorded on the JEOL GSX-400, 60 MHz spectrometer in acetone and TMS (tetramethylsilane) as an internal standard. The ^{1}H chemical shifts were reported as parts per million (ppm) downfield from TMS (Me_4Si). ^{1}H-NMR and IR spectra were consistent with the assigned structures. The elemental analysis (CHN analysis) was done on a CHN rapid analyzer. Purity of the compounds was checked by thin layer chromatography (TLC).

Synthesis of Benzimidazole Half gram (0.0046 mol) of *o*-phenylenediamine and 0.32 g (3 ml, 0.062 mol) of 90% formic acid was added in Erlenmeyer flask and the reaction mixture was homogeneously mixed. The mixture was heated at 20% for 80 s, the flask was then removed, cooled (up to room temperature) and 10% sodium hydroxide solution was added slowly, with constant stirring, until the mixture was just alkaline to litmus. The crude benzimidazole was filtered off and washed thrice with ice-cold water and dried. To decolorize, the crude product obtained was dissolved in boiling water, 0.2 g of decolorizing carbon was added and digested for 10 min then filtered rapidly at 10 °C. The product was filtered off, washed with cold water and dried at 100 °C. Recrystallized the product with methanol and weighed. (Conventionally synthesized by reported method.)[20] Colour: Dusty white, crystalline product obtained (yield 0.501 g, 91.75%). ^{1}H-NMR (acetone-d_6) δ: 8.23 (1H, d), 7.70—7.21 (4H, m), 5.0 (1H, d). IR (KBr) cm^{-1}: 3061, 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.

Synthesis of Methyl Benzimidazole Half gram (0.0028 mol) of *o*-phenylenediamine dihydrochloride (prepared as per the reported literature),[24] 3 ml of water and 0.5087 g (0.5 ml, 0.0085 mol) of acetic acid was added in Erlenmeyer flask and the mixture was heated at 20% for 80 s. The mixture was cooled (upto room temperature) and neutralized with concentrated ammonia solution. Crude methyl benzimidazole was filtered off, washed thrice with ice-cold water and dried, decolorized the crude product as earlier procedure, recrystallized with ethanol and weighed. (Conventionally synthesized by reported method.)[20] Colour: Pale yellowish (0.332 g, 89.01%). ^{1}H-NMR (acetone-d_6) δ: 7.70—7.21 (4H, m), 5.0 (1H, s), 2.4 (3H, s). IR (KBr) cm^{-1}: 3028, 1591, 1504, 1457, 1634, 1320, 1155. *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.

Synthesis of Phenyl Benzimidazole Half gram (0.0028 mol) of *o*-phenylenediamine dihydrochloride (prepared as per the reported literature),[24] 0.344 g (0.0028 mol) of benzoic acid and 6.99 g poly phosphoric acid (PPA) were added and mixed homogeneously. Mixture was heated trice at 20% for 1 min 30 s; each time the mixture was removed and stirred for few moments. Mixture was then cooled upto room temperature and neutralized with ice-cold 10% aqueous sodium carbonate solution. Solid product obtained was collected, dried at room temperature and recrystallized with aqueous methanol. (Conventionally synthesized by reported method.)[24] Colour: Light yellow crystalline (small crystal size), (0.461 g, 84.83 %). ^{1}H-NMR (acetone-d_6) δ: 7.70—7.21 (4H, m), 7.48—7.32 (5H, m), 5.0 (1H, s). IR (KBr) cm^{-1}: 3071, 1602, 1583, 1558, 1507, 1455, 1324, 1180, 1698. *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.

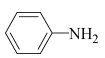
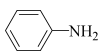
Synthesis of 2-(4-Aminophenyl)benzimidazole Half gram (0.0028 mol) of *o*-phenylenediamine dihydrochloride (prepared as per the reported literature),[24] 0.387 g (0.0028 mol) of *p*-amino benzoic acid (PABA) and 6.99 g poly phosphoric acid (PPA) were added and mixed homogeneously. The mixture was heated trice at 20% for 1 min 40 s; each time mixture was removed and stirred for few moments. The mixture was then cooled upto room temperature and neutralized with ice-cold 10% aqueous sodium carbonate. The obtained solid product was collected, dried at room temperature and recrystallized with aqueous methanol. (Conventionally synthesized by reported method.)[24] Colour: Yellowish white, crystalline (large needle shape) product was obtained. (0.5606 g, 94.80%). ^{1}H-NMR (acetone-d_6) δ: 7.70—7.26 (4H, m), 7.23 (2H, d), 6.7—6.6 (2H, d), 5.0 (1H, s), 4.0 (2H, s). IR (KBr) cm^{-1}: 3010, 1600, 1573, 1440, 1311, 1680, 1174, 3461, 3386. *m*/*z*: 209 (M^+). *Anal.* Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.31; H, 5.46; N, 20.30.

Synthesis of 2-(4-Chlorophenyl)benzimidazole Half gram (0.002 mol) of *o*-phenylenediamine dihydrochloride (prepared as per the reported literature),[24] 0.442 g (0.0028 mol) of *p*-chlorobenzoic acid and 6.99 g poly phosphoric acid (PPA) were added and mixed homogeneously. The mixture was heated trice at 20% for 90 s; each time the mixture was removed and stirred for little moment. Then the mixture was cooled upto room temperature and neutralized with ice-cold 10% aqueous sodium carbonate solution. Solid product obtained was collected and dried at room temperature and recrystallized with aqueous methanol. (Conventionally synthesized by reported method.)[21] Colour: White crystalline (small size crystal), (0.5724 g 88.63 %), ^{1}H-NMR (acetone-d_6) δ: 8.03—7.54 (4H, m), 7.42—7.33 (2H, d), 7.2—7.0 (2H, d), 5.0 (1H, s). IR (KBr) cm^{-1}: 3094, 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.

Results and Discussion

Benzimidazole and its 2-alkyl and aryl substituted derivatives were synthesized by conventional and microwave assisted methods. The synthesized compounds and their physicochemical properties are given in Tables 1 and 2. The structures of the synthesized compounds were confirmed by NMR, IR, Mass and elemental analysis. The results obtained from the spectroscopy confirm the structure of the synthesized compounds. The comparative data of the synthesized compounds are provided in Table 2. The reaction time for the

Table 1. Reactants and Solvents Used for Synthesis of Benzimidazole Derivatives by Conventional and Microwave Assisted Synthesis Method

S. No	R1	R2	Reactant I	Reactant II	A	Compound	Molecular formula
1	H	H	*o*-Phenylenediamine	Formic acid	—	Benzimidazole	$C_7H_6N_2$ (118.14)
2	H·HCl	CH_3	*o*-Phenylenediamine dihydrochloride	Acetic acid	Water	2-Methyl benzimidazole	$C_8H_8N_2$ (132.16)
3	H[a]		*o*-Phenylenediamine	Benzoic acid	PPA	2-Phenyl benzimidazole	$C_{13}H_{10}N_2$ (194.23)
	H·HCl		*o*-Phenylenediamine dihydrochloride				
4	H[a]		*o*-Phenylenediamine	*p*-Amino benzoic acid	PPA	2-(4-Aminophenyl) benzimidazole	$C_{13}H_{11}N_3$ (209.25)
	H·HCl		*o*-Phenylenediamine dihydrochloride				
5	H[a]		*o*-Phenylenediamine	*p*-Chloro benzoic acid	PPA	2-(4-Chlorophenyl) benzimidazole	$C_{13}H_9ClN_2$ (228.68)
	H·HCl		*o*-Phenylenediamine dihydrochloride				

a) Conventional method.

Table 2. Comparative Physicochemical Data of Conventional and Microwave Assisted Synthesized Compounds

Compound	Conventional synthesis				Microwave assisted synthesis			
	RT[a]	% Yield	mp °C (reported)	*Rf* value	RT	% Yield	mp (°C)	*Rf* value
Benzimidazole	2 h	80.22%	171—172 °C (171 °C)	0.575[b]	1 min 20 s	91.75%	172 °C	0.609[b]
2-(Methyl)benzimidazole	45 min	47.90%	177—180 °C (179 °C)	0.469[c]	1 min 20 s	89.01%	179 °C	0.468[c]
2-(Phenyl)benzimidazole	4 h	33.58%	238 °C (238 °C)	0.272[c]	4 min 30 s	84.83%	238 °C	0.276[c]
	—	—	—	—	8 min[d]	82.44%[d]	—	—
2-(Amino phenyl)benzimidazole	4 h	56.55%	248 °C (246 °C)	0.250[c]	5 min	94.80%	246 °C	0.265[c]
	—	—	—	—	8 min[d] 40 s	94.23%[d]	—	—
2-(Chloro phenyl)benzimidazole	4 h	43.37%	240—242 °C (241 °C)	0.304[c]	4 min 30 s	88.63%	242 °C	0.297[c]
	—	—	—	—	6 min[d] 30 s	87.84%[d]	—	—

a) Reaction time, *b*) ethyl acetate : *n*-hexane 7 : 3, *c*) ethyl acetate : *n*-hexane : water 7 : 2 : 1, *d*) reaction time and percentage yield of compounds synthesized from *o*-phenylenediamine in microwave method.

synthesis of benzimidazole derivatives by conventional method was 45 min to 4 h in comparison with the microwave heating (1—5 min), which reduced the time duration many fold. Approximately 96 to 98% was decreased reaction time and the yield obtained was increased by 10 to 50%. Use of reactant and their salt form were observed to have effect on yield and time of reaction, shown in Table 2. The salt form of the reactant reduced the reaction time approximately 30—50% than *o*-phenylenediamine itself in microwave assisted method. This may be due to interfacial polarization. As heating is very important for reactant to crossover the activation barrier and perform the reaction, microwave have made easy to do so.

Conclusion

From the study it was concluded that synthesis of benzimidazole and their 2-substituted derivative from microwave has reduced the reaction time from 96 to 98% and increase the yield near about 10 to 50%. The study also showed some remarkable inferences while the use of salt form of reactant (*o*-phenylenediamine dihydrochloride).

In the final product, no color impurities of *o*-phenylenediamine was observed.

The salt form of reactant allowed the homogeneous mixing of reaction mixture, while in *o*-phenylenediamine the mixing require continuous stirring which cause sticking of reactant on stirr.

The reaction completion time was reduced.

This study also concluded that the developed procedure for synthesis of compound benzimidazole derivatives through microwave is simple, increased purity and yields of product, ease of work up, simplicity and overall safety compared with reported conventional method.

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