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# 1,3-Dibromo 5,5-dimethylhydantoin (DBH)-Catalyzed Solvent-Free Synthesis of 2-arylbenzimidazoles under Microwave Irradiation

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**Abstract:** An expeditious synthesis of 2-aryl-benzimidazoles by the condensation of *o*-phenylenediamine with various arylaldehydes is described. This greener protocol is catalyzed by 1,3-Dibromo 5,5-dimethylhydantoin (DBH), and proceeds efficiently in the absence of any organic solvent under thermal condition and microwave irradiation in high yields.

**Keywords:** 1,3-Dibromo 5,5-dimethylhydantoin (DBH), Benzimidazoles, Microwave irradiation, Solvent free.

## Introduction

Benzimidazoles are very useful intermediates for the development of molecules of pharmaceutical and biological interest. Substituted benzimidazole derivatives have found applications in diverse therapeutic areas including antiulcers, antihyperten-sives, antivirals, antifungals, anticancers, and antihistaminics[1,2]. The widespread interest in benzimidazole containing structures has prompted extensive studies for their synthesis. There are two general methods for the synthesis of 2-substituted benzimidazoles. One is the coupling of *o*-phenylenediamines and carboxylic acids[3] or their derivatives (nitriles, imidates, or orthoesters), which often require strong acidic conditions and sometimes combine with very high temperatures (i.e., PPA, 180$^{o}$C)[4,5-6]. The other way involves a two-step procedure that includes the oxidative cyclodehydrogenation of aniline Schiff's bases, which are often generated in situ from the condensation of *o*-phenylenediamines and aldehydes[7-12]. However, suffer from longer reaction times, unsatisfactory yields, harsh reaction conditions and excessive use of reagents and catalysts. It is therefore important to find more convenient methods for the preparation of these compounds.

Microwave-assisted organic synthesis[13] (MAOS) has attracted considerable interest and is an important technique in green synthetic chemistry. It could help achieve high yields and clean reaction out comes at shorter action time. Organic solvent- free reaction conditions eliminate the toxicity and flammability issues associated with common solvents. Together,

solvent-free organic syntheses assisted by microwave irradiation (MW) have being regarded as environmentally benign methodologies.

## Experimental

All the reactions were carried out using a conventional (unmodified) microwave oven (LG, 230 V, ~50 Hz). Reactions were monitored on TLC by comparison with the samples prepared by known procedures. The Infrared spectroscopy (IR) spectra were recorded using a Shimadzu 435-U-04 spectrophotometer (KBr pellets) and the Nuclear magnetic resonance (NMR) spectra were obtained in using a 90 MHz JEOL FT NMR spectrometer. All melting points were determined on a Büchi 530 melting point apparatus and are reported uncorrected.

Microwave experiments were conducted using a CEM Discover monomode oven operating at 2450 MHz monitored by a PC computer, and temp. was maintained at a constant value by power modulation (0 – 300W). Stirring was provided by an *in situ* magnetic stirrer. Reactions were performed in open glass vessels (capacity 10 mL). Reaction conditions: power 300W; no solvent; ramp time 3 min; hold time 10 min; stirring on; temp. 145$^{o}$C.

*General Procedure for the Synthesis of 2-aryl-benzimidazoles (Method A)*

To a mixture of *o*-phenylenediamine (1 mmol), aldehyde (1 mmol) and 1,3-dibromo 5,5-dimethyl hydantoin (DBH) (0.12 mmol, 0.34 mg) was added and the mixture was inserted in an oil bath and heated at 50$^{o}$C for the appropriate time (Table **1**). Completion of the reaction was indicated by Thin Layer Chromatography (TLC). After which dichloromethane (10 ml) was added to the mixture and left aside for a few minutes, the solid thus separated was recrystallized from methanol or subjected to silica gel column chromatography to get the pure product/s.

*General Procedure for the Synthesis of 2-aryl-benzimidazoles (Method B)*

A mixture of *o*-phenylenediamine (1 mmol), aldehyde (1 mmol) and 1,3-dibromo 5,5-dimethyl hydantoin (DBH) (0.12 mmol, 0.34 mg) was taken in the special open glass vessel. The mixture was thoroughly mixed, and the tube was then subjected to microwave irradiation according to the above protocol. (see Table 1). After which dichloromethane (10 ml) was added to the mixture and left aside for a few minutes, the solid thus separated was recrystallized from methanol or subjected to silica gel column chromatography to get the pure product/s.

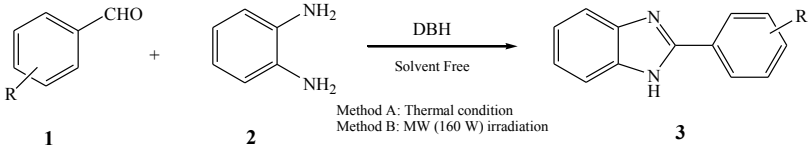
The products were characterized on the basis of their physical and spectral analysis and by direct comparison with literature data [14-17].

## Results and Discussion

In continuation with the search for simple non-hazardous methods for the transformations in organic synthesis using halogenating agents[18-26], herein we report a highly versatile and efficient synthesis of 2-aryl-benzimidazoles **3** from *o*-phenylenediamine, aldehyde and catalytic amounts of 1,3-dibromo 5,5-dimethyl hydantoin (DBH) under solvent-free and microwave conditions in high yields (Scheme 1).

To find out the optimum quantity of 1,3-dibromo 5,5-dimethyl hydantoin (DBH), the reaction of *o*-phenylenediamine and benzaldehyde was carried out under thermal solvent-free conditions (Method A) using different quantities of DBH (Table 1). As shown this table, 0.12 mmole of DBH gave excellent yield in 95 as can be seen from Table **1**. Thus, we prepared arrange of benzimidazoles under the optimized reaction conditions: *o*-phenylenediamine (1 mmol) and aldehyde (1 mmol) in the presence of DBH (0.12 mmol). A

series of benzimidazoles were prepared in high to excellent yields by two methods (A, B) (Table 2).




**Scheme 1**

**Table 1**. The effect of amount of DBH on the reaction of *o*-phenylenediamine and benzaldehyde under thermal solvent free conditions.

| Entry | Catalyst (mmol) | Time (min) | Yield[a] (%) |
|---|---|---|---|
| 1 | 0 | 120 | 0 |
| 2 | 0.05 | 85 | 51 |
| 3 | 0.1 | 60 | 87 |
| 4 | 0.12 | 45 | 95 |
| 5 | 0.15 | 45 | 95 |
| 6 | 0.20 | 45 | 95 |

[a]Yields refer to the pure isolated products.

To account for the facile formation of benzimidazoles, the following mechanism (Scheme 2) is proposed. The reaction between an aldehyde and a diamine leads to the formation of Schiff base (**I**) which is stabilized by catalyze. Intermolecular attack by the second amino group on C=N double bond facilitates the formation of hydro-benzimidazole (**II**) which undergoes subsequent air oxidation [23] to give the desired benzimidazole as the final product.

**Table 2**. DBH catalyzed synthesis of benzimidazoles.

| Entry | Product[a] | R | Method A Time/Yields (%)[b] | Method B Time/Yields (%)[b] | M.p., $^{o}$C (Lit.)[c] |
|---|---|---|---|---|---|
| 1 | **3a** | H | (45 min/95) | (5 min/93) | 287-288(288-190) |
| 2 | **3b** | 4-Me | (48 min/93) | (6 min/94) | 278-280 (277-279) |
| 3 | **3c** | 3-Me | (49 min/92) | (8 min/93) | 215-217 (217-219) |
| 4 | **3d** | 4-OMe | (52 min/94) | (5 min/90) | 226-228 (227-228) |
| 5 | **3e** | 3-OMe | (54 min/89) | (6 min/95) | 211-213 (210-210.4) |
| 6 | **3f** | 3,4-$OMe_2$ | (58 min/89) | (9 min/89) | 178-180 (178-179) |
| 7 | **3g** | 4-N(Me)2 | (52 min/90) | (7 min/93) | 250-251 (252-254) |
| 8 | **3h** | 4-$NO_2$ | (44 min/94) | (9 min/92) | 297-299 (298-300) |
| 9 | **3i** | 3-$NO_2$ | (41 min/93) | (8 min/89) | 205-207 (204-206) |
| 10 | **3j** | 2-$NO_2$ | (43 min/95) | (6 min/90) | 169-170 (168-170) |
| 11 | **3k** | 4-Cl | (45 min/94) | (5 min/94) | 191-193 (192-293) |
| 12 | **3l** | 2-Cl | (47 min/92) | (6 min/92) | 156-158 (155-156) |
| 13 | **3m** | 3-F | (43 min/93) | (7 min/93) | 221-223 (220-222) |
| 14 | **3n** | 4-F | (42 min/96) | (6 min/92) | 202-203 (203-205) |
| 15 | **3o** | 2-OH | (40 min/94) | (7 min/95) | 235-236 (236-237) |

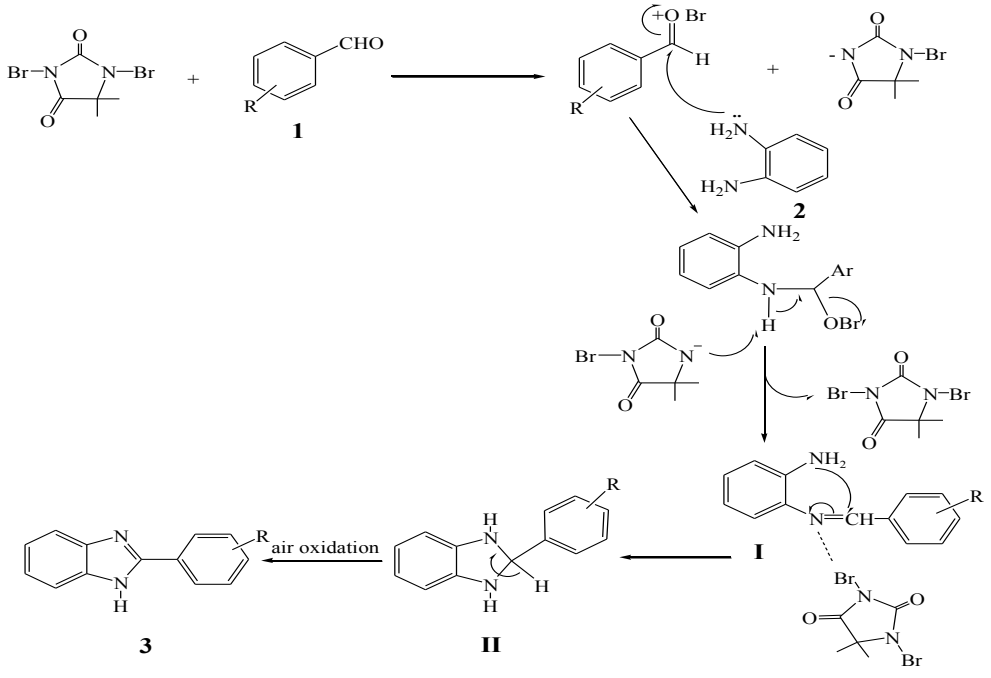
a) Isolated yields. b) All the products are known, characterized by IR, NMR spectral analysis and compared with the authentic samples. c) Melting points of compounds are consistent with reported values [14-16,27].

The compares the efficiency of DBH (time, yield, reaction conditions) with the efficiency of some other catalysts used in the synthesis of benzimidazoles (Table 3). It clearly shows that the presented method, using DBH as the catalyst, is simple, efficient and comparable with many catalytic systems for the synthesis of benzimidazoles derivatives.

**Table 3**. Comparison of efficiently various catalysts in the synthesis of benzimidazoles.

| Entry | Catalyst | Condition | Time (min)[h] | Yield (%) | Reference |
|---|---|---|---|---|---|
| 1 | DBH | Solvent-free/50 $^{o}$C | (45) | 95 | This work |
| 2 | DBH | Solvent-free/MW | (5) | 93 | This work |
| 3 | CAN (5 mol %) | PEG/50 $^{o}$C | [2] | 98 | 28 |
| 4 | Dowex 50 W | Water/70 $^{o}$C | [8] | 83 | 29 |
| 5 | $Me_2S^+BrBr^-$ | MCN/r.t | [5] | 85 | 10 |
| 6 | Polyaniline sulfate | $CH_2CH_2CL_2$/r.t | [2] | 92 | 12 |
| 7 | HCl | Solvent-free/MW | (10) | 93 | 4 |
| 8 | $SiO_2$-Pr-$SO_3H$ | Solvent-free/r.t | [1-2] | 90 | 30 |
| 9 | $NaHSO_3$ | DMAc/MW | (10) | 88 | 31 |
| 10 | $SiO_2$-$FeCl_3$ | $H_2O_2$/150 $^{o}$C | (30) | 95 | 32 |

The advantages or the characteristic aspects of the method described in this paper in comparison with other previously reported ones are the following: the yields of products were better than the previous reported yields and in addition, the catalyst DBH is inexpensive, has no moisture sensitivity, and no special measures are required for the reaction.




**Scheme 2**

## Conclusion

The present methodology shows that 1,3-dibromo 5,5-dimethyl hydantoin (DBH) is an efficient catalyst in the one-pot synthesis of benzimidazole derivatives. The main advantages of the presented protocol are mild, clean and environmentally benign reaction conditions, as well as the high yields. Furthermore, this method is also expected to find application in organic synthesis due to the low cost of the reagent. It is believed that this method will be a useful addition to modern synthetic methodologies.

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