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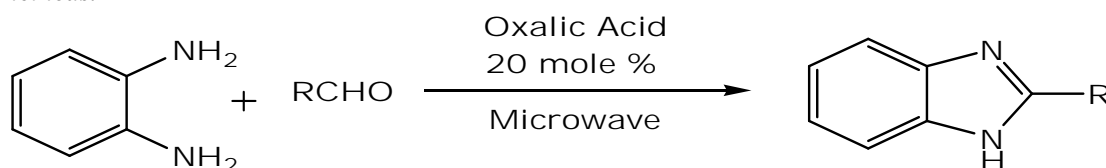
Microwave Assisted Synthesis of Benzimidazoles Catalysed by Oxalic Acid

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Abstract: A microwave assisted one-pot synthesis of benzimidazoles from 1, 2 phenylenediamine and aldehyde in the presence of oxalic acid as a catalyst is described. Advantage of this microwave technique, use the inexpensive and readily available catalyst, reaction time was greatly shortened and the products were obtained in higher yields with easier workup than conventional heating methods.

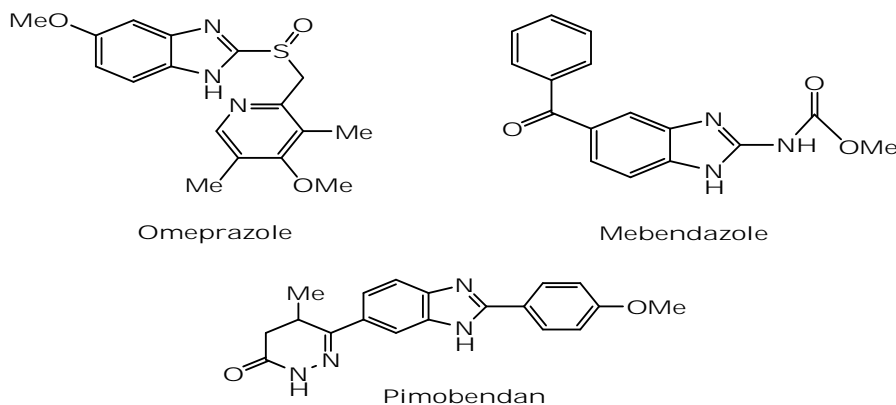


Keywords: Benzimidazole, Oxalic Acid, Microwave assisted synthesis, Catalyst, phenylenediamine, aromatic aldehyde.

I. INTRODUCTION

Benzimidazoles represent one of the biggest groups of heterocyclic compounds and have attracted a great deal of interest over the decades due to their wide and potent biological and medicinal activities (1). Benzimidazole is a heterocyclic aromatic organic bicyclic compound formed by the fusion of benzene and imidazole ring. Benzimidazole moiety is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities including antiulcer, antitumor, antiviral, anti-inflammatory, analgesic, anti-histamine, antioxidant, anti-proliferative, anti-allergic, anti-kinase and anti-cancer activities. They are also inhibitors of photosynthesis, aldose reductase and antagonist of neurotransmitter receptors. They also are found to exhibit appreciable herbicidal activity (2-4). The most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B12 (5).

There are many drugs based on benzimidazoles currently in the market such as rabeprazole (anti-ulcer), pimozide (antipsychotic), telmisartan (antihypertension), omeprazole (proton pump inhibitor), pimobendan (ionodilator), and mebendazole (antihelminthic) (1).



Most of the described methods for the synthesis of benzimidazoles make use of volatile organic solvents and involve solid-phase synthesis via o-nitroanilines or the condensation of o-phenylenediamines with carboxylic acid derivatives, aldehydes and aryl halides. More recently, cleaner protocols have been described, including solvent-free conditions and the use of water and ionic liquid as green solvents (6). However, most of these protocols use expensive and toxic reagents and/or long reaction times. Thus the

development of clean, general, and selective routes to synthesize benzimidazole, including the use of new catalysts, alternative or non-solvents, and non-classical energy sources continues to be an important field of research.

Due to their importance, many synthesis strategies have been developed. The most popular synthesis approaches generally involve the condensation of an arylenediamine with a carboxylic acid or its derivative under harsh dehydrating reaction conditions (7). Another method is the condensation of an aldehyde with arylenediamine (8). Very recently, literature survey reveals several methods for synthesis of benzimidazole and its derivatives using hypervalent iodine as oxidant (9), oxalic acid (10), H₂O₂/HCl (11), TiCl₄ (12), PPA (13), SOCl₂/SiO₂ (14), L-Proline (15), Sulphamic acid (16) and Zeolite (17). Many of these methods have drawbacks such as expensive reagents, oxidation processes, and long reaction times. In some cases, 2-substituted and 1, 2-disubstituted benzimidazole were generated simultaneously with poor selectivity.

In connection with our ongoing research for the development of simple and efficient methods for synthesis of benzimidazole compounds, now we report microwave assisted one pot synthesis of 2-aryl substituted benzimidazole compounds (18) using oxalic acid (5 mol %) as a catalyst.

The use of microwave irradiation as a source of heat in synthetic chemistry has been achieved a promising method of increasing productivity and quality and reducing reaction time (19). In 1986 first use microwave for the synthesis of benzimidazoles. It has become a focal point in chemical synthesis in recent years in terms of sustainable and green chemistry for improved resource management. Since 1986, various substituted benzimidazole derivatives have been synthesized through microwave heating (20).

The reaction time required for the synthesis of benzimidazole derivatives was reduced to minutes by this method compared to conventional synthesis, which required up to four hours of heating to complete the reaction. Furthermore, it was found that the application of microwave irradiation increased yields by 10–50%

Here in, we report a microwave assisted synthesis using oxalic acid as a catalyst.

II. MATERIAL AND METHODS

Microwave assisted synthesis of benzimidazole derivatives using Oxalic acid as a catalyst

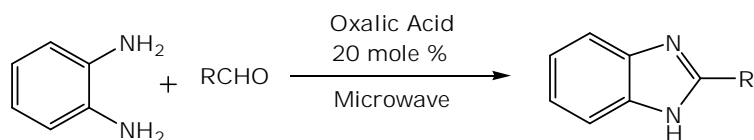
A. Experimental

The chemicals used were of Laboratory Reagent grade and Analytical Reagent grade and were purchased from Sigma-Aldrich and E. Merck Ltd. India. The glass wares used during the study were of Borosil made. The solvents were distilled prior to their use. All reactions were monitored with silica gel thin layer chromatography (TLC) plates and using hexane and ethyl acetate as solvent system. Aldehyde (1.0 mmol) and *o*-phenylenediamine (1.0 mmol) were thoroughly mixed in THF (2 mL), then oxalic acid as a catalyst (0.2 mmol) was added, and the mixture was placed under microwave irradiation for a period of 2-3 minutes. The reaction progress was monitored over silica gel TLC plates using hexane and ethyl acetate (80: 20) solvent system. After completion of reaction, the mixture was cooled to room temperature. The reaction mixture was added dropwise with vigorous stirring into a solution of Na₂CO₃ (0.2 mmol) in H₂O (20 mL). Solid product was collected by filtration, washed with H₂O and dried. In cases where gummy material precipitated, the product was extracted into EtOAc, the organic phase was washed with H₂O, brine and the dried over Na₂SO₄. Removal of solvent afforded product. The obtained product were identified by their spectral (NMR and IR) data (18).

III. RESULT AND DISCUSSION

Microwave assisted synthesis of benzimidazole from aromatic aldehyde and 1, 2 phenylenediamine were studied by using oxalic acid as catalyst in dimethylformamide as solvent (scheme 1). To the best of our knowledge, there are no examples on the use of oxalic acid as a catalyst in the formation of benzimidazole derivatives by microwave irradiation method.

oxalic acid is a catalyst, which is less costly and decreased the reaction time and increased the yield of the product. This method could be easily practiced in laboratories within 5 minute. Oxalic acid can act as a strong organic acid due to containing two carboxylic group joined directly.



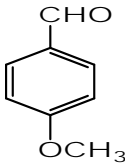
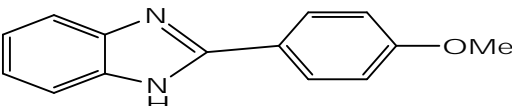
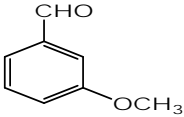
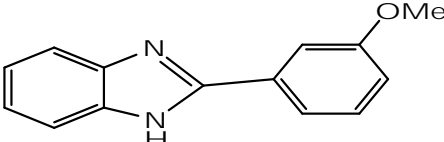
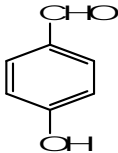
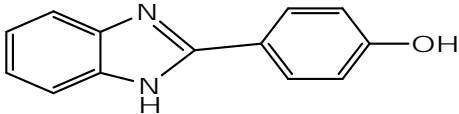
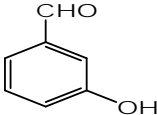
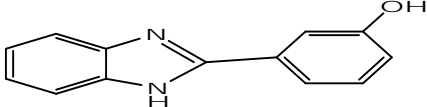
R=C₆H₅, 2-ClC₆H₄, 4-ClC₆H₄, 4-NO₂C₆H₄, 3-NO₂C₆H₄, 4-CH₃OC₆H₄, 3-CH₃OC₆H₄, 4-FC₆H₄, 4-CH₃CHO, 4-OHC₆H₄, 3-OHC₆H₄.

1) Scheme 1: Synthesis of benzimidazole derivatives using oxalic acid as a catalyst

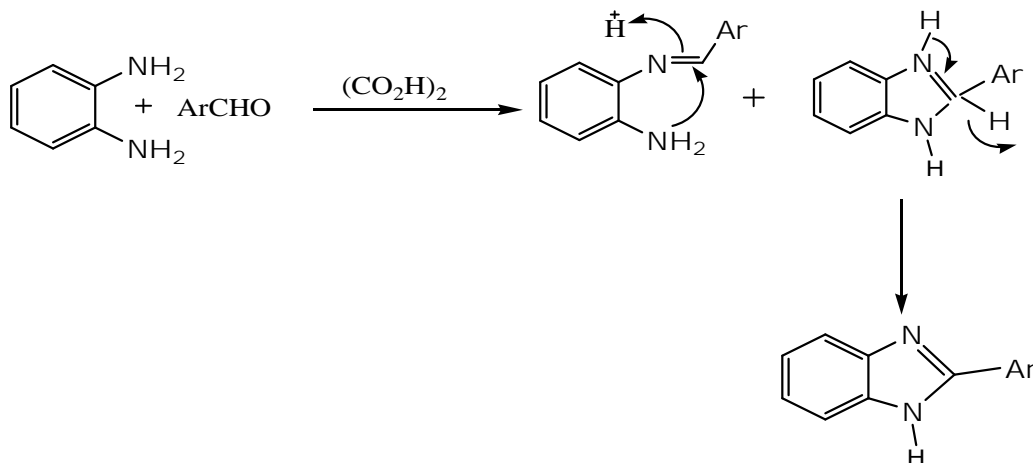
The compounds were prepared in good yield by microwave assisted synthesis of benzimidazole by aromatic aldehyde and 1, 2 phenylenediamine using oxalic acid as catalyst in tetrahydrofuran (THF). Better yields are obtained using oxalic acid catalyst and time duration of reaction is also less. Work up of reaction is also easy. The compounds synthesized and their yields are presented in **Table 1**.

Table 1: Synthesis of benzimidazole derivatives catalysed by Oxalic acid

Entry	Aldehyde	Product		Yield
1.			a1	95%
2.			a2	83%
3.			a3	84%
4.			a4	88%
5.			a5	83%
6.			a6	84%
7.			a7	80%

8.			a8	86%
9.			a9	83%
10.			a10	81%
11.			a11	81%

We can explain the synthesis of formation of benzimidazoles product using oxalic acid as a catalyst, from aromatic aldehyde, 1, 2 phenylenediamine and THF according to mechanism (10). This mechanism proposed the synthesis of the 1, 2-disubstitued bezimidazoles, it may involve the iminium catalysed formation of an N,N'-dibenzylidene-o-phenylenediamine, protonation, and ring closure to give five membered ring either in sequential or a concerted manner (10).



2) *Scheme 2*: Proposed mechanism for the formation of disubstitued benzimidazoles catalysed by Oxalic acid (10)

In conclusion we have reported here a facile method for the synthesis of benzimidazole derivatives by the condensation of 1, 2 phenylenediamine and aldehyde using oxalic acid as a catalyst. Moreover catalyst works well under microwave irradiation. Conventional methodology involves simply stirring of reaction mixture. The reaction time (3-4 hours) for conventional method is reduced to minutes (2-4 minute) under microwave irradiation.

IV. ACKNOWLEDGEMENT

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A. Spectral Characterisation Data

- 1) A1: IR (KBr): 3424, 3041, 1743, 1629 cm^{-1} .
 $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 6.09 (bs, 1H, NH), 6.87 (d, 2H, PH), 6.99 (d, 2H, PH), 7.08 (t, 1H, PH), 7.31 (m, 2H, PH), 7.51 (m, 2H, PH).
- 2) A2: IR (KBr): 3181, 1520, 1436, 1348, 975, 740 cm^{-1} .
 $^1\text{HNMR}$ (CDCl_3 , 400 MHz) δ 6.09 (bs, 1H, NH), 9.0 (s, 1H, PH), 8.62 (d, 1H, PH), 8.5 (d, 1H, Ph), 8.30 (t, 1H, Ph), 7.9- 7.4 (m, 4H, Ph).
- 3) A3: IR (KBr): 3552, 1715, 1600, 1550, 1450, 848, 740 cm^{-1} .
 $^1\text{H NMR}$ (CDCl_3 , 400 MHz) 8.15-8.22(m, 2H, Ph), 7.16-7.23(m, 2H, Ph), 6.7-6.9(m, 4H, Ph), 6.09 (bs, 1H, NH).
- 4) A4: IR (KBr): 3021, 1611, 1444, 1275, 963, 747 cm^{-1} .
 $^1\text{HNMR}$ (CDCl_3 , 400 MHz) δ 7.5-7.9 (m, 4H, Ph), 7.22 (d, 2H, Ph), 7.28 (d, 2H, Ph), 2.39 (s, 3H, CH_3), 6.07 (bs, 1H, NH).
- 5) A6: IR (KBr): 3442, 1598, 1580, 1429 cm^{-1} .
 $^1\text{H NMR}$ (CDCl_3 , 400 MHz) 8.18(d, 2H, Ph), 7.45(d, 2H, Ph) 7.19-7.25 (m, 2H, Ph), 7.12(d, 2H, Ph), 6.02 (bs, 1H, NH).
- 6) A7: IR (KBr): 2851, 1647, 1442, 1398, 1297, 974, 946 cm^{-1} .
 $^1\text{HNMR}$ (CDCl_3 , 400 MHz) δ 7.5-7.9 (m, 4H, Ph), 7.2-7.3 (m, 4H, Ph), 6.07 (bs, 1H, NH).
- 7) A8: IR (KBr): 3294, 3103, 1184, 1588 cm^{-1} .
 $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 3.70 (d, 3H, OCH_3), 6.12 (bs, 1H, NH), 6.94 (d, 2H, Ph), 6.98(d, 2H, ph), 7.20(d, 2H, Ph), 7.58 (d, 2H, Ph).
- 8) A10: IR (KBr): 3379, 3211, 3078, 1461 cm^{-1} .
 $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 6.06 (bs, 1H, NH), 6.82 (d, 2H, Ph), 6.98 (d, 2H, Ph), 7.21 (d, 2H, Ph), 7.52 (d, 2H, Ph).

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