Three component one pot synthesis of 1, 2-disubstituted benzimidazoles using $Ticl_4$ as a catalyst in the microwave irraditation

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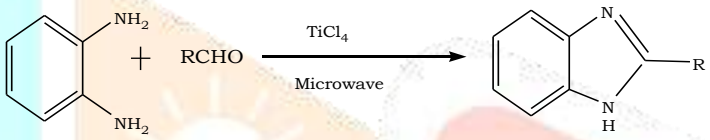
***Abstract*: In this study we reported three component one pot synthesis of benzimidazole derivatives using $TiCl_4$ as a catalyst for rapid, efficient and environment friendly synthesis. Benzimidazole derivatives constitute a class of compound exhibiting a number of important biological and pharmacological properties.**

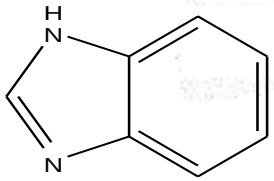


***Keywords:* benzimidazole derivatives, catalyst, microwave irradiation, three component, one pot synthesis.**

I. Introduction: Benzimidazole derivatives plays very important role in medicinal chemistry due to their important pharmacophore and a privileged structure (1). Now-days benzimidazoles, formed by the fusion of phenyl and imidazole ring, is a moiety of choice which possesses many medicinal properties.

Benzimidazole have versatile biological activity including anti-inflammato, analgesic, anti-fungal, anti-microbial, antihelmintic, anti-cancer, anti-asthmatic, anti-diabetic, anti-tubercular, antiprotozoal, antiviral, anti-HIV activities etc (2). N-ribosyl-dimethyl benzimidazole is the most important benzimidazole compound found in nature, which serve as an axial ligand for cobalt in vitamin 12.

(i). Chemistry of benzimidazole: Benzimidazole is a heterocyclic aromatic organic compound. It is bicyclic in nature. It consist the fusion of benzene and imidazole ring.



benzimidazole

Benziminazoles are also known as 1, 3-benzodiazoles [3, 4]. These have both acidic and basic properties. Due to the presence of NH group benzimidazoles is relatively strong acidic and also weakly basic. Benzimidazoles have the capacity to form salts. Benzimidazoles with unsubstituted NH groups represent fast prototropic tautomerism, which leads to equilibrium mixtures of asymmetrically substituted compounds [5].

In recent years, green chemistry has received more attention for synthesizing medicinally important compounds including benzimidazole and their derivatives. Microwave assisted Synthesis of chemical compounds is widely used to drug discovery as a clean process. Many research papers have been published in the area of one pot microwave assisted organic synthesis. In this process, under controlled heating of microwave in sealed vessel condition has significantly reduced reaction time whereas significantly increased product yield and purity of product by reducing unwanted side reactions appears in conventional synthetic methods [6, 7]. In this study we reported three component one pot synthesis of benzimidazole derivatives using $TiCl_4$ as a catalyst for rapid and efficient synthesis.

II. Material and Methods: Microwave assisted synthesis of benzimidazole derivatives using $TiCl_4$ as a catalyst

(i). Experimental

In recent time, we have shown $KHSO_4$ [8] and Ionic Liquid [9] can be used as promoters and catalysts for the synthesis of benzimidazoles. So we tried to synthesize benzimidazoles using an organocatalyst. In this paper, $TiCl_4$ was used for the synthesis of 2-arylsubstituted benzimidazoles by the condensation of aryl aldehyde with *o*-phenylenediamine.

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. Column chromatography was performed using Merck silica gel (100—120mesh). The obtained product were identified by their spectral (NMR and IR) data.

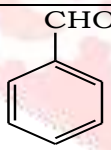
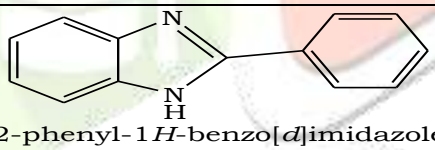
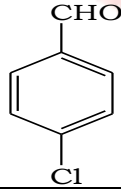
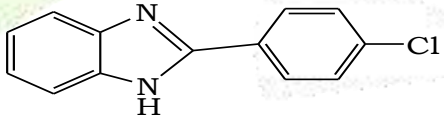
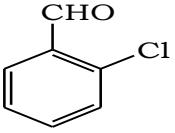
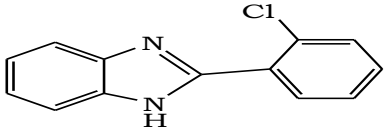
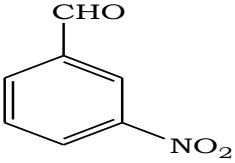
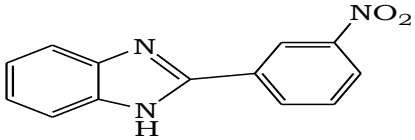
Aldehyde (0.1 mmol) and *o*-phenylenediamine (0.1 mmol) were thoroughly mixed in THF (2 mL), then $TiCl_4$ (0.2 mmol) was added, and the mixture was placed in microwave under irridation for a period of 3 minutes. (monitored the by TLC). When the reaction was finished, the solution was cooled to room temperature. The reaction mixture was added dropwise with vigorous stirring into a mixture of Na_2CO_3 (0.2 mmol) and H_2O (20 mL). In cases where the product precipitated as a free flowing solid, it was collected by filtration, washed with H_2O and dried. In cases where gummy material precipitated the product was extracted with EtOAc, the organic phase was washed with H_2O, brine and dried over (Na_2SO_4). Evaporation of solvent gave the crude product, which was purified by column chromatography over silica gel (hexane : ethyl acetate, 3:1) to afford the corresponding benzimidazole.

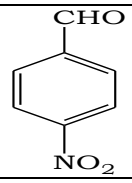
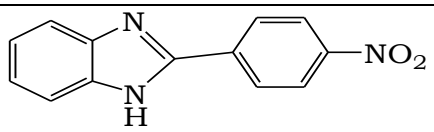
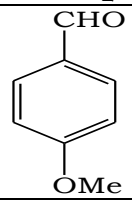
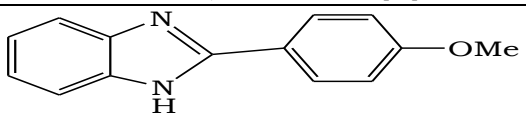
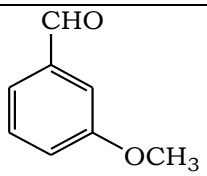
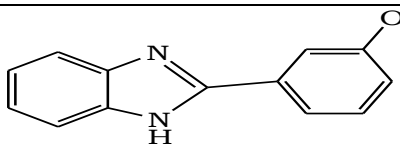
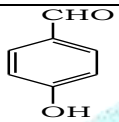
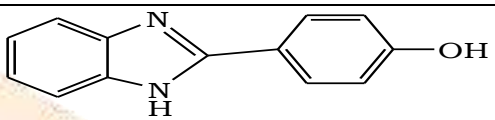
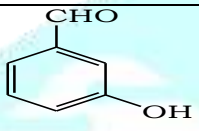
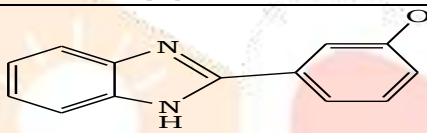
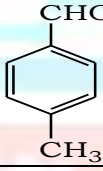
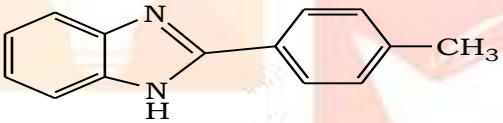
III. Result and Discussion: Micorwave assisted synthesis of benzimidazole from aromatic aldehyde and 1, 2 phenylenediamine were studied by using $Ticl_4$ as catalyst in tetrahydrofuran as solvent (scheme 1). To the best of our knowledge, there are no examples on the use of $TiCl_4$ as a catalyst in the formation of benzimidazole derivatives by microwave irradiation method.

Figure 1: synthesis of benzimidazole derivatives using $TiCl_4$ as a catalyst

R= 2-ClC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$, 3-$CH_3OC_6H_4$, 2-OHC_6H_4, 3-OHC_6H_4, 4-OHC_6H_4, 4-$CH_3C_6H_4$, 4-FC_6H_4

Table 1: Synthesis of benzimidazole derivatives

Entry	Aldehyde	Product		Yield
1		 2-phenyl-1*H*-benzo[*d*]imidazole	**B1**	78%
2		 2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazole	**B2**	88%
3		 2-(2-chlorophenyl)-1*H*-benzo[*d*]imidazole	**B3**	70%
4		 2-(3-nitrophenyl)-1*H*-benzo[*d*]imidazole	**B4**	87%

5		 2-(4-nitrophenyl)-1*H*-benzo[*d*]imidazole	**B5**	88%
6		 2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole	**B6**	86%
7		 2-(3-methoxyphenyl)-1*H*-benzo[*d*]imidazole	**B7**	83%
8		 4-(1*H*-benzo[*d*]imidazol-2-yl)phenol	**B8**	81%
9		 3-(1*H*-benzo[*d*]imidazol-2-yl)phenol	**B9**	81%
10		 2-*p*-tolyl-1*H*-benzo[*d*]imidazole	**B10**	82%

The compounds were prepared in good yield by microwave assisted synthesis of benzimidazole by aromatic aldehyde and 1, 2 phenylenediamine using $TiCl_4$ as catalyst in Tetrahydrofuran (THF). Titanium (IV) chloride is moderately strong Lewis acid with many application evidenced in conversion of ketones to N-alkylimines, in Aldol condensation of aryl ketones with aryl aldehyde, in Michael addition of silyl enol ethers to S, Y-enones etc. Conventional method for synthesis of benzimidazole derivatives earlier have been carried out by using $TiCl_4$ [10]. Better yield are obtained using $TiCl_4$ catalyst and time duration of reaction is also less under microwave irradiation. This technique is very simple, rapid, environment friendly and efficient. Workup of the reaction is also very easy. The compounds synthesized and their yields are presented in Table 1.

Acknowledgement

This work was supported by the G. B. Pant University of Agriculture and Technology. Thanks are due to SAIF, Punjab University, India for providing IR and NMR spectra.

Spectral Characterisation Data

1. **B1:** IR (KBr): 3422, 3040, 1741, 1629 cm^{-1}.
^1H NMR ($CDCl_3$, 400MH_Z) δ 6.05 (bs, 1H, NH), 6.89 (d, 2H, PH), 6.99 (d, 2H, PH), 7.08 (t, 1H , PH), 7.31 (m, 2H, PH), 7.51 (m, 2H, PH).

2. **B2:** IR (KBr): 3445, 1591, 1580, 1429 cm^{-1}.
^1H NMR ($CDCl_3$, 400MHZ) 8.16(d, 2H, Ph), 7.41(d, 2H, Ph) 7.19-7.28 (m, 2H, Ph), 7.12(d, 2H, Ph), 6.02 (bs, 1H, NH).

3. **B3:** IR (KBr): 2851, 1643, 1441, 1396, 1297, 973, 943 cm^{-1}.
^{1}HNMR ($CDCl_3$, 400MHz) δ 7.5-7.8 (m, 4H, Ph), 7.2-7.4 (m, 4H, Ph), 6.07 (bs, 1H, NH).

4. **B4:** IR (KBr): 3184, 1521, 1435, 1343, 972, 743 cm^{-1}.
^{1}HNMR ($CDCl_3$, 400MH_Z) δ 6.01 (bs, 1H, NH), 9.0 (s, 1H, PH), 8.66 (d, 1H, PH), 8.3 (d, 1H, Ph), 8.31 (t, 1H, Ph), 7.4- 7.9 (m, 4H, Ph).

5. **B5:** IR (KBr): 3552, 1715, 1600, 1550, 1450, 848, 740 cm^{-1}.
^1H NMR ($CDCl_3$, 400MH_Z) 8.15-8.23(m, 2H, Ph), 7.16-7.25(m, 2H, Ph), 6.7-6.9(m, 4H, Ph), 6.05 (bs, 1H, NH).

6. B6: IR (KBr): 3291, 3102, 1185, 1589 cm-^{1}
^{1}H NMR ($CDCl_3$, 400MH_Z) δ 3.71 (d, 3H, OCH3), 6.10 (bs, 1H, NH), 6.93 (d, 2H, Ph), 6.95(d, 2H, ph), 7.21(d, 2H, Ph), 7.58 (d, 2H, Ph).

7. B8: IR (KBr): 3378, 3213, 3079, 1467 cm^{-1}
^{1}H NMR ($CDCl_3$, 400MHZ) δ 6.06 (bs, 1H, NH), 6.84 (d, 2 H, Ph) , 6.99 (d, 2H, Ph), 7.21(d, 2H, Ph), 7.56 (d, 2H, Ph).

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