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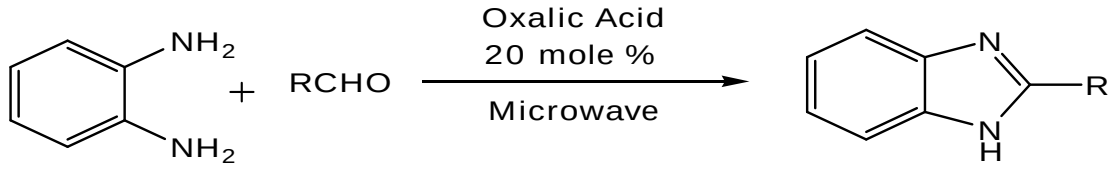
Microwave Assisted Synthesis of Benzimidazoles Catalysed by Oxalic Acid

Jyoti Pandey Tripathi[1], Virendra Kumar Kasana[2]
[1] *Department Of Chemistry, College of Basic Sciences and Humanities G. B. P. U. & T. Pantnagar- 263145 (India)*
[2] *Changed affilation, Bipin Tripathi kumaoun Institute Of Techanology, Dwarahat, Almora 263653*

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.***

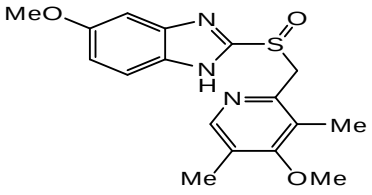


Keywords: Benzimidazole, Oxalic Acid, Microwave assisted synthesis, Catalyst, phenylenediamine, aromatic aldehyde.

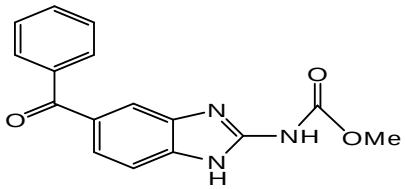
I. INTRODUCTION

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 bicycilc compound are 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).

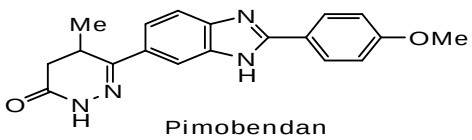
There are many drugs based on benzimidazoles currently in the market such as rabeprazole (anti-ulcer), pimozide (antipsychotic), telmisartan (antihypertension), omeprazole (proton pump inhibitor), pimobendan (ionodilator), and mebendazole (antihelmintic) (1).



Omeprazole



Mebendazole



Pimobendan

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 a 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 reveales several methods for synthesis of benzimidazole and its derivatives using hypervalent iodine as oxidant (9), oxalic acid (10), H_2O_2/HCl (11), $TiCl_4$ (12), PPA (13), $SOCl_2/SiO_2$ (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

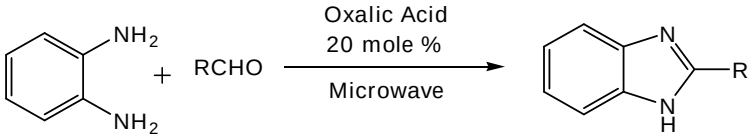
A. Experimental

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. Aldhyde (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 Na_2CO_3 (0.2 mmol) in H_2O (20 mL). Solid product was collected by filtration, washed with H_2O and dried. In cases where gummy material precipitated, the product was extracted into EtOAc, the organic phase was washed with H_2O, brine and the dried over Na_2SO_4. Removal of solvent afforded product. The obtained product were identified by their spectral (NMR and IR) data (18).

III. RESULT AND DISCUSSION

Micorwave 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.

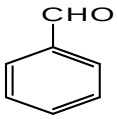
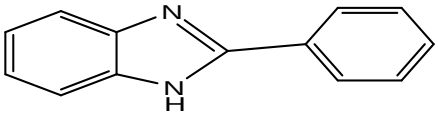
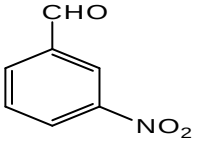
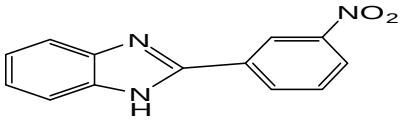
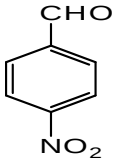
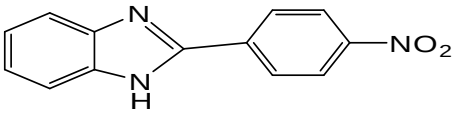
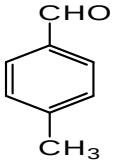
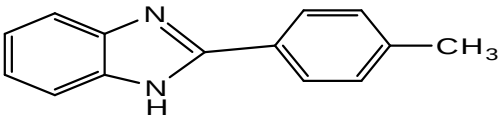
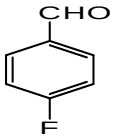
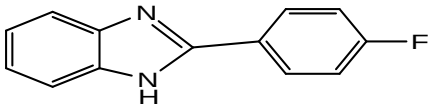
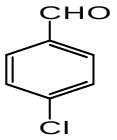
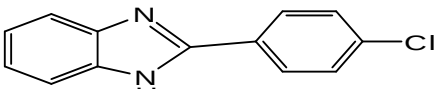
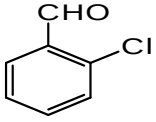
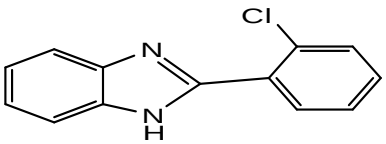


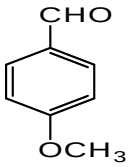
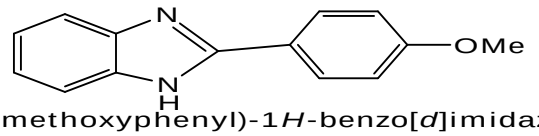
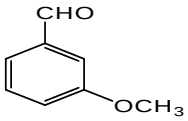
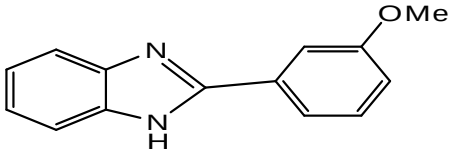
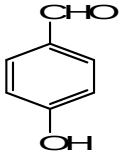
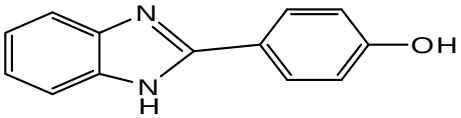
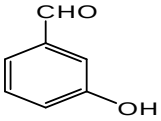
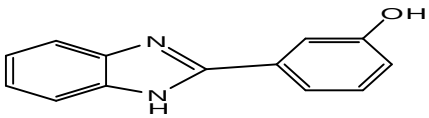
R=C_6H_5, 2-ClC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$, 3-$CH_3OC_6H_4$, 4-FC_6H_4, 4-CH_3CHO, 4-OHC_6H_4, 3-OHC_6H_4.

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

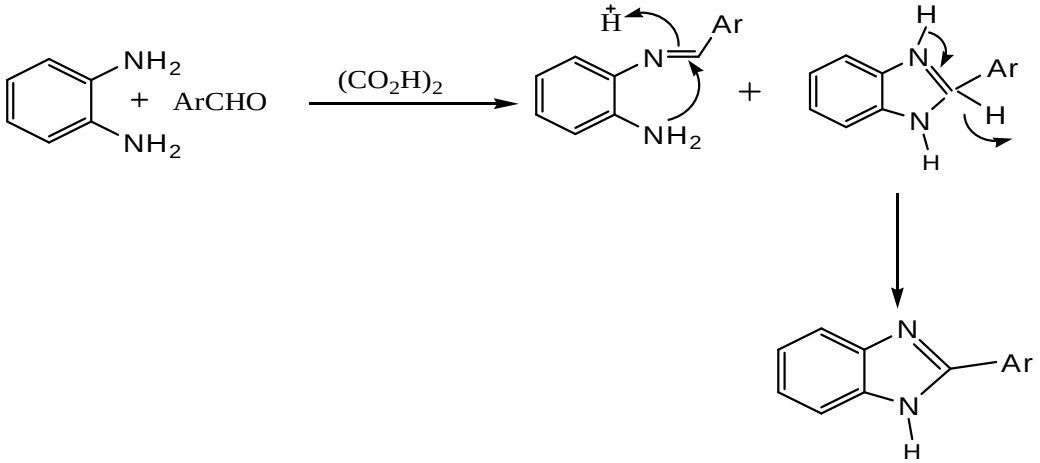
The compounds were prepared in good yield by microwave assisted synthesis of benzimidazole by aromatic aldehyde and 1, 2 phenylenediamine using oxalic acid as catalyst in tetrahydrofuran (THF). Better yields are obtained using oxalic acid catalyst and time duration of reaction is also less. Work up of 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.		 2-phenyl-1*H*-benzo[*d*]imidazole	a1	95%
2.		 2-(3-nitrophenyl)-1*H*-benzo[*d*]imidazole	a2	83%
3.		 2-(4-nitrophenyl)-1*H*-benzo[*d*]imidazole	a3	84%
4.		 2-*p*-tolyl-1*H*-benzo[*d*]imidazole	a4	88%
5.		 2-(4-fluorophenyl)-1*H*-benzo[*d*]imidazole	a5	83%
6.		 2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazole	a6	84%
7.		 2-(2-chlorophenyl)-1*H*-benzo[*d*]imidazole	a7	80%

8.		2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole 	a8	86%
9.		2-(3-methoxyphenyl)-1*H*-benzo[*d*]imidazole 	a9	83%
10.		4-(1*H*-benzo[*d*]imidazol-2-yl)phenol 	a10	81%
11.		3-(1*H*-benzo[*d*]imidazol-2-yl)phenol 	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 Oxlic 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

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.

A. Spectral Characterisation Data

1) A1: IR (KBr): 3424, 3041, 1743, 1629 cm^{-1}.
^1H NMR ($CDCl_3$, 400MH_Z) 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}HNMR ($CDCl_3$, 400MH_Z) 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}.
^1H NMR ($CDCl_3$, 400MH_Z) 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}HNMR ($CDCl_3$, 400MHz) 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}.

^1H NMR ($CDCl_3$, 400MHZ) 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}HNMR ($CDCl_3$, 400MHz) δ 7.5-7.9 (m, 4H, Ph), 7.2-7.3 (m, 4H, Ph), 6.07 (bs, 1H, NH).

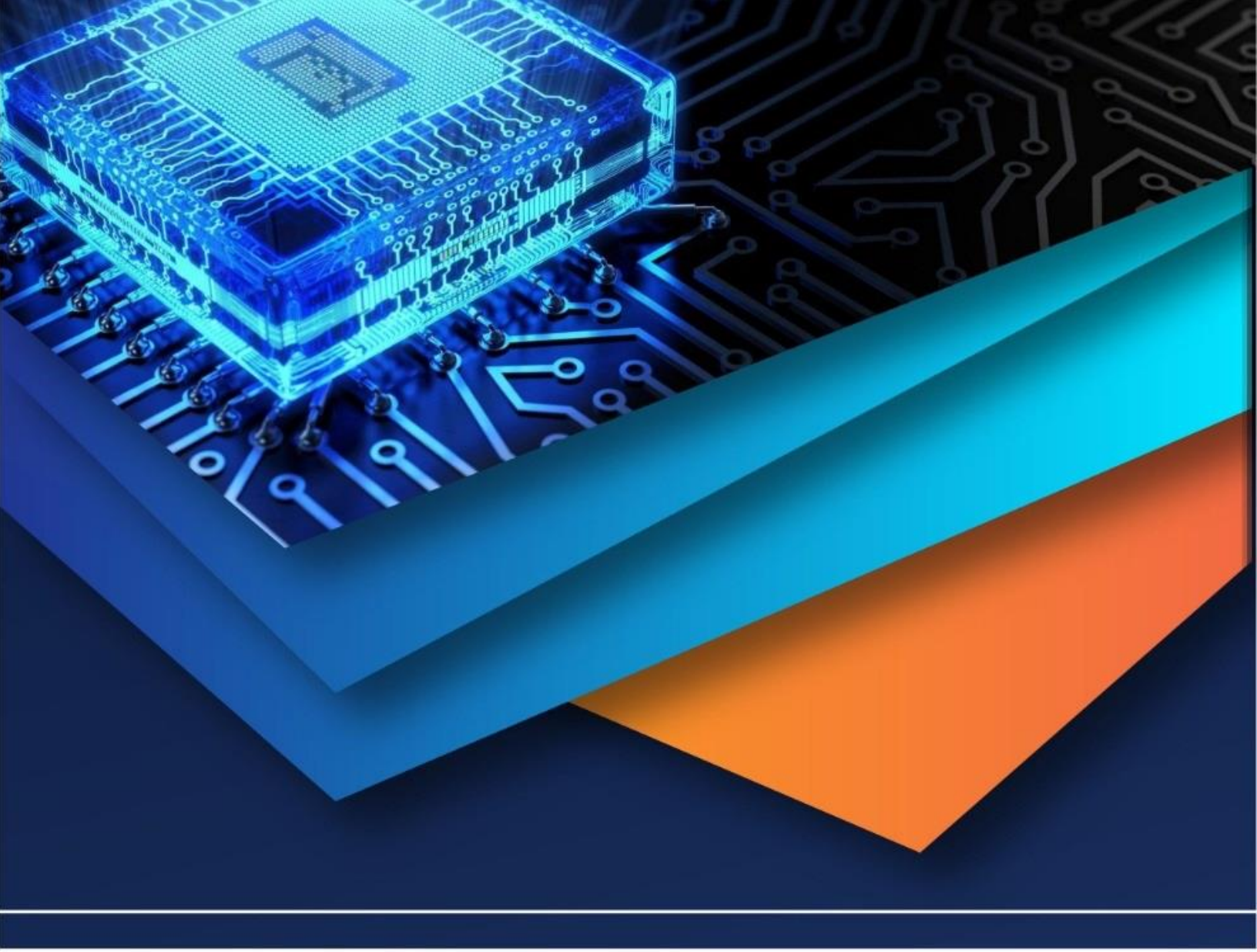
7) A8: IR (KBr): 3294, 3103, 1184, 1588cm-^{1}
^1H NMR ($CDCl_3$,400MH_Z) δ 3.70 (d, 3H, OCH3), 6.12 (bs, 1H, NH), 6.94 (d, 2H, Ph), 6.98(d, 2H, ph), 7.20(d, 2H, Ph), 7.58 (d, 2H, Ph).

8) A10: IR (KBr): 3379, 3211, 3078, 1461 cm^{-1}
^1H NMR ($CDCl_3$, 400MHZ) δ 6.06 (bs, 1H, NH), 6.82 (d , 2 H , Ph) , 6.98 (d , 2 H, Ph), 7.21(d , 2 H , Ph), 7.52 (d, 2H, Ph).

REFERENCES

[1] M. Alamgir, D. S. C. Black, and N. Kumar, "Synthesis, Reactivity and Biological Activity of Benzimidazoles," Top Heterocycl Chem., 9, 87–118, 2007
[2] Erhardt, P. W. "In search of the digitalis replacement," J. Med. Chem., 30 (2), 231-237, 1987
[3] B. E. Tomczuk, C. R. Jr Taylor, L. M. Moses, D. B. Sutherland, Y. S. Lo, D. N. Johnson, W. B. Kinnier and B. F. Kilpatrick, "2-Phenyl-3H-imidazo[4,5-b]pyridine-3-acetamides as non-benzodiazepine anticonvulsants and anxiolytics," J. Med. Chem., 34(10), 2993-3006, 1991.
[4] A. A. Spasov, I. N. Yozhitsa, L. I. Bugaeva and V. A. Anisimova, "Benzimidazole derivatives: Spectrum of pharmacological activity and toxicological properties (a review),"Pharm. Chem. J. 33(5), 232–243, 1999.
[5] C. Zimmer and U. Wahnert, "Nonintercalating DNA-binding ligands: specificity of the interaction and their use as tools in biophysical, biochemical and biological investigations of the genetic material," Mol. Biol., 47 (1), 31-112, 1986.
[6] G. L. Gravatt, B. C. Baguley, W. R. Wilson and W. A. Denny, "DNA-Directed Alkylating Agents. 6. Synthesis and Antitumor Activity of DNA Minor Groove-Targeted Aniline Mustard Analogs of Pibenzimol," J. Med. Chem., 37, 4338-4345, 1994
[7] K. J. Soderlind, B. Gorodetsky, A. K. Singh, N. Bachur, G. G. Miller and J. W. Lown, "Bis-benzimidazole anticancer agents: targeting human tumour helicases," Anti-cancer Drug Design, 14(18), 19-36, 1999
[8] H. Xiangming, M. Huiqiang, and W. Yulu "p-TsOH Catalyzed synthesis of 2-arylsubstituted benzimidazoles," ARKIVOC. (xiii) 150-154, 2007.
[9] J. S. Kim, B. Gatto, C. Yu, A. Liu, .L F. Liu and E. J. LaVoie, "Substituted 2,5'-Bi-1H-benzimidazoles: Topoisomerase I Inhibition and Cytotoxicity," J. Med. Chem., 39, 992-998, 996
[10] A. Y. Chen, C Y.u, B. Gatto and L F Liu "DNA minor groove-binding ligands: a different class of mammalian DNA topoisomerase I inhibitors" Proc Natl Acad Sci U S A., 90(17), 8131–8135, 1993.
[11] J. M. Woynarowski, M. McHugh, R. D. Sigmund and T. A. Beerman, "Modulation of topoisomerase II catalytic activity by DNA minor groove binding agents distamycin, Hoechst 33258, and 4',6-diamidine-2-phenylindole" Mol. Pharmacol., 35(2), 177-182, 1989.
[12] T. Roth, M. L. Morningstar, P. L. Boyer, S. H. Hughes, R. W. Buckheit and C. J. Michejda, "Synthesis and Biological Activity of Novel Nonnucleoside Inhibitors of HIV-1 Reverse Transcriptase. 2-Aryl-Substituted Benzimidazoles" J. Med. Chem. 40, 4199-4207, 1997
[13] H. A. Barker, R. D. Smyth, H. Weissbach, J. I. Toohey, J. N. Ladd and B. E. Volcani. "Isolation and properties of crystalline cobamide coenzymes containing benzimidazole or 5, 6-dimethylbenzimidazole," Journal of Biological Chemistry, 235(2), 480- 488, 1960
[14] L. M. Dudd, E. Venardou, E. G. Verdugo, P. Licence, A. J. Blake, C. Wilson and M. Poliakoff. "Synthesis of benzimidazoles in high-temperature water" Green Chem. 5, 187-192. 2003
[15] F. M. Moghaddam, G. R. Bardajee, H. Ismaili and S. M. D. Taimoory. "Facile and Efficient One-Pot Protocol for the Synthesis of Benzoxazole and Benzothiazole Derivatives using Molecular Iodine as Catalyst," Synth. Commun., 36 (16), 2543-2548, 2006
[16] L. H. Du and Y. G. Wang. "A Rapid and Efficient Synthesis of Benzimidazoles Using Hypervalent Iodine as Oxidant," Synthesis., 5, 675-678, 2007
[17] N. D. Kokare, J. N. Sangshetti and D. B. Shinde. "One-Pot Efficient Synthesis of 2-Aryl-1-arylmethyl-1H-benzimidazoles and 2,4,5-Triaryl-1H-imidazoles Using Oxalic Acid Catalyst," Synthesis. 18, 2829-2834, 2007
[18] B. Kiumars, K. M. Mehdi, K. Iman "A Simple and Efficient One-Pot Synthesis of 2-Substituted Benzimidazoles," Synthesis. 4, 547-550, 4, 2007
[19] R. R. Nagawade and D. B. Shinde, "$TiCl_4$ Promoted synthesis of benzimidazole derivatives," Indian Journal of Chem., 46b, 349, 2007
[20] J. Lu, B. Yang and Y. Bai. "Microwave irradiation synthesis of 2-substituted benzimidazoles using PPA as a catalyst under solvent-free conditions," Synth Comm., 32, 3703-3709, 2002

[21] A. Ben, A. K. Bougrin and M. Soufiaoui.
[22] R. Varala, A. Nasreen, R. Enugala and S. R. Adapa. "L-Proline catalyzed selective synthesis of 2-aryl-1-arylmethyl-1H-benzimidazoles" Tetrahedron. Lett. 48(1), 69-72, 2007.
[23] Z. H. Zhang, T. S. Li and J. J. Li. "A Highly Effective Sulfamic Acid/Methanol Catalytic System for the Synthesis of Benzimidazole Derivatives at Room Temperature," Monatsh Chem., 138 (1), 89-94, 200
[24] M. M. Heravi and Mahzood Tajbakhsh. "Zeolites. Efficient and Eco-friendly Catalysts for the Synthesis of Benzimidazoles," Monatsh Chem., 137(2), 175-179, 2006
[25] N. D. Kokare, R. R. Nagawade, V. P. Rane and D. B. Shinde. "Organophosphorus Esters of 1-Hydroxy-2-phenylbenzimidazole: Synthesis and Utilization as Novel Peptide Coupling Reagents" Synthesis. 766-772, 2007.
[26] R. R. Nagawade, V. V. Khanna, S. S. Bhagwat and D. B. Shinde."
[27] S. S. Bahekar, S. A. Kotharkar and D. B. Shinde. "
[28] Richard Gedye, Frank Smith, Kenneth Westaway, Humera Ali and John Rousell "
[29] K Bougrin, M. Soufiaoui. "Nouvelle voie de synthèse des arylimidazoles sous irradiation micro-ondes en "milieu sec"" Tetrahedron Lett. 36, 3683-3683, 1995.



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