One-pot synthesis of Benzimidazole derivatives catalyzed by stannous Chloride under solvent-free condition

KHANDU D WARAD[1] R P PAWAR[2] CHANDRASHEKHAR G DEVKATE[3] RAJIV V KHOBARE[4]

[1]*Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431004, India*

[2]*Department of Chemistry, Govt. Vidarbha Institute of Science and Humanities, Amravati-444604, India*

[3]*Department of Chemistry, Indraraj Arts, Commerce and Science College Sillod, Aurangabad-431112, India*

[4]*Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431004, India*

Abstract:

The present work is mainly designed to synthesize a variety of new benzimidazole derivatives from condensation of 1, 2-phenylendiamine and aldehydes catalyzed by anhydrous stannous chloride. The salient features of this method include simple procedure, mild conditions, no waste produced (only by-product being water), easy purification, moderate to good yields of products and high generality.

Keywords: benzimidazole, stannous chloride, one pot synthesis

Introduction:

These heterocyclic compounds and their derivatives occupy an important place in medicinal chemistry due to the fact that they occur in a wide variety of natural and synthetic compounds and are essential to life in various ways.[1]

Out of several heterocycles benzimidazole is a fused aromatic imidazole ring system where a benzene ring is fused to the 4 and 5 positions of an imidazole ring and serves as an important class of bioactive molecules in the field of drugs and pharmaceuticals.[2]

Benzimidazole nucleus has wide spread presence in numerous categories of therapeutic agents such as antimicrobials[3], antivirals[4], antiparasites [5], anticancer, [6] anti-inflammatory [7], antioxidants [8], proton pump inhibitors [9], antihypertensives [10], anticoagulants [11], immunomodulators [12], and antidiabetics [13]. Varied substitutents around the benzimidazole nucleus have also provided a wide spectrum of biological activities.

There are many reports for synthesis benzimidazoles like heterocyclization of o-phenylenediamine and carboxylic acids, aldehydes, alcohols and nitriles. The limitations of these methods includes that these methods requires strong acid, high temperature, and sometimes photoirradiation conditions, precious metal salts and oxidants.[14]. Green chemistry is involving utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in synthesis chemical products is an important ecofriendly solution to above problem. [15]

In the present research we have focused on a synthesis variety of new benzimidazole derivatives from condensation of 1, 2-phenylendiamine and aldehydes catalyzed by anhydrous stannous chloride.

2. RESULTS AND DISCUSSION

To optimize the reaction conditions, we have carried out the model reaction of 1,2-phenylendiamine and aldehydes using stannous chloride as a catalyst by using water or ethanol as a solvent or without solvent, at room temperature, reflux and by using ultrasound irradiations. Results obtained are presented in Table 1. High yields were obtained by using ultrasonication method and utilizing water as a green solvent in short time. Effect of various solvent on synthesis of compound are listed in table 2. In order to understand amount of catalyst to obtain maximum yield we have carried out model reaction with different amount of catalyst (Table 3) and found that 10 mol % of catalyst is sufficient, further increasing the amount of catalyst does not affect the yield.

The present method involves condensation of 1,2-phenylendiamine and heterocyclic aldehydes catalyzed by anhydrous stannous chloride to obtain benzimidazole derivatives.

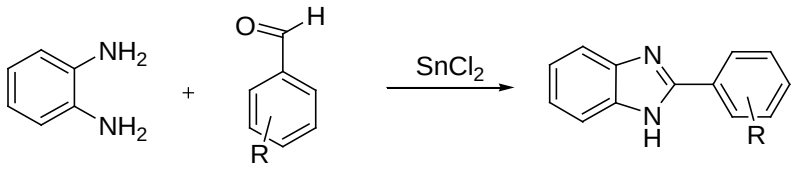
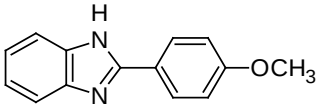
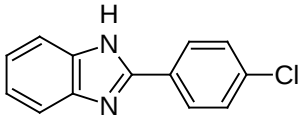
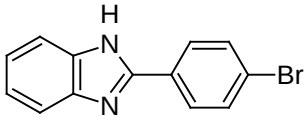
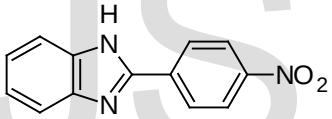
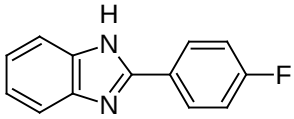
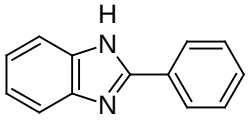
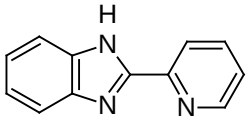
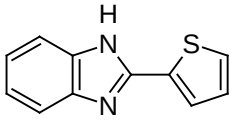


Fig 1: General scheme for synthesis of benzimidazoles

Sr.No.	Compound No.	Name of Compound	Boiling/Melting Point ^{0}C	%Yield
1.	**3a**	 2-(4-methoxyphenyl)-1H-benzimidazole	**172**	**95**
2.	**3b**	 2-(4-chlorophenyl)-1*H*-benzimidazole	**303 °**	**93**
3.	**3c**	 2-(4-bromophenyl)-1*H*-benzimidazole	**299 °C**	**95**
4.	**3d**	 2-(4-nitrophenyl)-1*H*-benzimidazole	**281.16**	**92**
5.	**3e**	 2-(4-fluorophenyl)-1*H*-benzimidazole	**255-257**	**86**
6.	**3f**	 2-phenyl-1*H*-benzimidazole	**293-296**	**94**
7.	**3g**	 2-(pyridin-2-yl)-1*H*-benzimidazole	**221-225**	**97**
8.	**3f**	 2-(thiophen-2-yl)-1*H*-benzimidazole	**230**	**96**

Representative spectra of 2-(4-Nitrophenyl)-1*H*-benzimidazole:

Yellow crystals, IR (KBr): 1338, 1516 (NO2), 1607 (C=N), 3436 (NH) cm-1. 1H NMR (600 MHz, DMSO-d6) δ 13.31 (s, 1H), 8.44-8.41 (m, 4H), 7.73-7.66 (m, 2H), 7.28 (s, 2H).13C NMR (150 MHz, DMSO-d6) δ 149.46, 148.26, 136.50, 127.85, 124.76. HRMS (ESI) Calc. for C13H10N3O2 [M+H]+: 240.0768, found: 240.0768.

Table 2: Effect of various solvent on synthesis of compound 3.

Entry	**Solvent** **Time,**	**Temperature,** **0C/)))))))**	**Min**	**Yield,** **%**
1.	H2O	r.t.	360	86
2.	H2O	Reflux	240	84
3.	H2O	)))))))	45	92
4.	EtOH	r.t.	378	70
5.	EtOH	Reflux	300	68
6.	EtOH	)))))))	50	80
7.	No Solvent	r.t.	420	42
8.	No Solvent	Reflux	480	46
9.	No Solvent	)))))))	120	35

Table 3: Optimization of catalyst for synthesis of benzimidazole derivatives

Serial no	**Amount of stannous Chloride , mol %**	**Percent yield**
1.	**No catalyst**	**10**
2.	**5**	**52**
3.	**10**	**92**
4.	**20**	**92**
5.	**30**	**92**

EXPERIMENTAL:

All reagents and chemicals were purchased from SD Fine or spectrochem chemical company, Mumbai, India. All reagents and chemicals were of analytical grade and used without further purification. Sonication was performed in ultrasonic cleaner with a frequency of 25 KHz and nominal power 250 W. The reaction temperature was controlled by addition or removal of water from ultrasonic bath.

General procedure for the synthesis of substituted benzimidazoles

In 100 mL round bottom flask substituted 1, 2-phenylendiamine and substituted benzaldehydes (1 mol), stannous chloride (10 % mol) were taken in 20 mL water as a green solvent.

The resulting reaction mixture was sonicated for a period as indicated in Table 1. The progress of reaction was monitored by using TLC. After completion of reaction, the solid product obtained was filtered, washed with water and recrystallized from ethanol to afford the pure product. All the products were confirmed by comparing their melting points, IR and 1H NMR data with literature data.

CONCLUSION:

In conclusion, we have achieved benzimidazole synthesis by one pot multicomponent procedure using green synthetic protocol under ultrasound irradiation technique, using water as a green solvent and stannous chloride as a catalyst. Striking features of this method are short reaction time, easy work up procedure, water solvent, use of ultrasound waves, atom economy

References:

(1) Rajam, S.; P, C. R. S.; G, B. D. A.; Ranjith, R. Review Article The Chemistry and Biological Significance of Imidazole , Benzimidazole , Benzoxazole , Tetrazole and Quinazolinone Nucleus. *J. Chem. Pharm. Res.* **2016**, *8* (5), 505–526.

(2) Thakuria, H.; Das, G. An Expeditious One-Pot Solvent-Free Synthesis of Benzimidazole Derivatives. *Arkivoc* **2008**, *2008* (15), 321–328. https://doi.org/10.3998/ark.5550190.0009.f28.

(3) Singh, N.; Pandurangan, A.; Rana, K.; Anand, P.; Ahamad, A.; Tiwari, A. K. Benzimidazole: A Short Review of Their Antimicrobial Activities. *Int. Curr. Pharm. J.* **2012**, *1* (5), 110–118. https://doi.org/10.3329/icpj.v1i5.10284.

(4) Tomei, L.; Altamura, S.; Bartholomew, L.; Biroccio, A.; Ceccacci, A.; Pacini, L.; Narjes, F.; Gennari, N.; Bisbocci, M.; Incitti, I.; et al. Mechanism of Action and Antiviral Activity of Benzimidazole-Based Allosteric Inhibitors of the Hepatitis C Virus RNA-Dependent RNA Polymerase. *J. Virol.* **2003**, *77* (24), 13225–13231. https://doi.org/10.1128/jvi.77.24.13225-13231.2003.

(5) Navarrete-Vazquez, G.; Cedillo, R.; Hernandez-Campos, A.; Yepez, L.; Hernadez-Luis, F.; Valdez, J.; Morales, R.; Cortes, R.; Hernandez, M.; Castillo, R. Synthesis and Antiparasitic Activity of 2-(Trifluoromethyl)-Benzimidazole Derivatives. *Bioorg. Med. Chem. Lett.* **2001**, *11* (2), 187–190.

(6) Yadav, S.; Narasimhan, B.; Kaur, H. Perspectives of Benzimidazole Derivatives as Anticancer Agents in the New Era. *Anticancer. Agents Med. Chem.* **2016**, *16* (11), 1403–1425.

(7) Lazer, E. S.; Matteo, M. R.; Possanza, G. J. Benzimidazole Derivatives with Atypical

Antiinflammatory Activity. *J. Med. Chem.* **1987**, *30* (4), 726–729.

(8) Cole, E. R.; Crank, G.; Salam-Sheikh, A. Antioxidant Properties of Benzimidazoles. *J. Agric. Food Chem.* **1974**, *22* (5), 918. https://doi.org/10.1021/jf60195a022.

(9) Iwahi, T.; Satoh, H.; Nakao, M.; Iwasaki, T.; Yamazaki, T.; Kubo, K.; Tamura, T.; Imada, A. Lansoprazole, a Novel Benzimidazole Proton Pump Inhibitor, and Its Related Compounds Have Selective Activity against Helicobacter Pylori. *Antimicrob. Agents Chemother.* **1991**, *35* (3), 490–496. https://doi.org/10.1128/AAC.35.3.490.

(10) Serafin, B.; Borkowska, G.; Glowczyk, J.; Kowalska, I.; Rump, S. Potential Antihypertensive Benzimidazole Derivatives. *Pol. J. Pharmacol. Pharm.* **1989**, *41* (1), 89–96.

(11) Wienen, W.; Stassen, J.-M.; Priepke, H.; Ries, U. J.; Hauel, N. Antithrombotic and Anticoagulant Effects of the Direct Thrombin Inhibitor Dabigatran, and Its Oral Prodrug, Dabigatran Etexilate, in a Rabbit Model of Venous Thrombosis. *J. Thromb. Haemost.* **2007**, *5* (6), 1237–1242. https://doi.org/10.1111/j.1538-7836.2007.02526.x.

(12) Kim, M. K.; Shin, H.; Park, K.; Kim, H.; Park, J.; Kim, K.; Nam, J.; Choo, H.; Chong, Y. Benzimidazole Derivatives as Potent JAK1-Selective Inhibitors. *J. Med. Chem.* **2015**, *58* (18), 7596–7602. https://doi.org/10.1021/acs.jmedchem.5b01263.

(13) Aboul-Enein, H. Y. Benzimidazole Derivatives as Antidiabetic Agents. *Med. Chem. (Los. Angeles).* **2015**, *5* (7), 318–325. https://doi.org/10.4172/2161-0444.1000280.

(14) Ajani, O. O.; Aderohunmu, D. V.; Ikpo, C. O.; Adedapo, A. E.; Olanrewaju, I. O. Functionalized Benzimidazole Scaffolds: Privileged Heterocycle for Drug Design in Therapeutic Medicine. *Arch. Pharm. (Weinheim).* **2016**, 475–506. https://doi.org/10.1002/ardp.201500464.

(15) Anastas, P. T. Introduction: Green Chemistry. *Chem. Rev.* **2007**, *107* (6), 2167–2168. https://doi.org/10.1021/cr0783784.