



Propylene Glycol: A Recyclable Solvent System for the Synthesis of Benzimidazole Derivatives Using ZnCl₂ as an Catalyst

Mahajan Tushar^{1*}, Kaneria Dhimant M², Upadhyay Jay S² and Sarvaiya Jayrajsinh¹

1. Department of Pharmacy, NIMS University, Jaipur, Rajasthan, India

2. Noble Pharmacy College, Junagadh, Gujarat, India

Email: mahajan.tushar2020@gmail.com

Received on 7th January and finalized on 10th February 2013.

ABSTRACT

Zinc chloride efficiently catalysed the synthesis of benzimidazole derivatives from *o*-phenylenediamine and aldehydes in PPG. This method provides a novel route for the synthesis of benzimidazoles in good yields with little catalyst loading. The recovery and the successful reutilization of the solvent system are also presented. Moreover, the easy set-up and purification tasks of this sustainable method make it appealing for bulk industry applications.

Keywords: Green synthesis, Zinc chloride, PPG, OPD, benzimidazoles, recyclability.

INTRODUCTION

Benzimidazole is a heterocyclic aromatic organic compound and bicyclic in nature which consists of the fusion of benzene and imidazole. Various studies have confirmed as a moiety of choice which possesses many pharmacological properties. Most of the members of this family have wide applications in Medical Chemistry such as antimicrobial and antibacterial effects[1], anti allergic activity[2], HIV inhibitors[3], anti viral effect[3], antiparasitic effect[4], anti hypertensive agents[5], cardiotoxic activity[6], anti ulcer activity[7], antiproliferative activity[8], anti-inflammatory activity[9], analgesic activity[10], antioxidant activity[11], antiprotozoal activity[12], anti diabetic activity[13], diuretic activity[14], androgen receptor antagonist[15], anti convulsing agents[16].

A number of methods have been developed for the synthesis of substituted benzimidazole derivatives. In recent years, solvent-free synthesis of benzimidazoles under microwave irradiation using Yb(OTf)₃, KSF clay, PPA, Na₂SO₄, K-10 clay, metal halide supported alumina and solid support have been reported[17]. Various oxidative and catalytic reagents such as sulfamic acid, I₂, DDQ, air, oxone, FeCl₃·6H₂O, In(OTf)₃, Yb(OTf)₃, Sc(OTf)₃, KHSO₄, IL, nitrobenzene, 1,4 – benzo quinine, tetracyano ethylene, benzofuroxan, MnO₂, Pb(OAc)₄, NaHSO₃, Na₂S₂O₅, DMP, NH₄VO₃ have been employed[17]. Benzimidazole derivatives can be synthesized by another catalysts such as CAN, *p*-TsOH, KHSO₄, CuPy₂Cl₂, polyphosphoric acid, mineral acids, boric acid, *p*-TSA, Dowex 50W, SSA, solid acid scolecite, YCl₃, Zn(OAc)₂, *N*-halosuccinamide (X = Cl, Br, I), Yb(OTf)₃, PEG-100, (NH₄)H₂PW₁₂O₄₀, bismuth chloride, mercury chloride, ionic liquids, AMA, TBAF, H₂O₂/ SiO₂-FeCl₃, HBF₄-SiO₂ and MoO₃/CeO₂-ZrO₂ using solvents like ethanol, methanol, DMSO, THF, DMF, CHCl₃, HCl, polyphosphoric acid, CH₂Cl₂, DCM, CH₃CN, H₂O₂, acetic acid[17]. However, in above some reported methods suffer from one or more drawbacks such as prolonged reaction times, use of environmentally unfavorable solvents and frequently low yields. Thus,

the development of a new method for the synthesis of benzimidazole derivatives would be highly desirable. The solvent-free organic synthesis have offered more advantages as compared to their homogeneous counterparts due to the growing concern for the influence of organic solvent on the environment as well as on human health, economical demands and simplicity in the processes. Various catalysts like as boric acid[18], Bf_3OEt_2 [19], SABA[17], PSSA[20], DBH[21], ammonium salts[22], glycerol[23], sulfonic acid functionalized silica ($\text{SiO}_2\text{-Pr-SO}_3\text{H}$)[24], $\text{P}_2\text{O}_5\text{-SiO}_2$ [25], $\text{Ku}[\text{Fe}(\text{CN})_6]$ [26], TsOH-SiO_2 [27], $\text{Zn}(\text{OAc})_2$ [28], FePO_4 [29], TBAF[30] have been used for solvent free methods. Recently, the use of recyclable solvent such as PEG developed in the synthesis of various benzimidazole derivatives [31]. Hence, now a day's research is mainly focused on Green Chemistry.

Organic synthesis on a large scale, compared to the laboratory scale, involves disadvantages such as use of volatile organic solvents, unsatisfactory product yields, critical product isolation procedures, expensive and detrimental metal precursors, harsh reaction conditions and also require tedious workup leading to the generation of a large amount of toxic waste. Such limit their use under the aspect of environmentally benign processes. Therefore, the development of efficient and environmental friendly green chemical processes is a major challenge for chemists in organic synthesis. Hence, Green Chemistry is interested for research and alternative innovations on many practical aspects of organic synthesis[32-34]. These methods involve use of solvent free method or use of recyclable organic solvents. The present work reports that the use of propylene glycol as best recyclable solvent for the synthesis of benzimidazole derivatives.

MATERIALS AND METHODS

All chemicals were purchased from sigma-Aldrich and Lancaster and were used without further purification. All reactions and purity of 2-aryl benzimidazole derivatives were monitored by thin layer chromatography (TLC) using aluminium plates coated with silica gel (Merck) using 20% ethyl acetate, 80% petroleum ether as an eluent. The isolated products were further purified by column-chromatography using silica gel (100–200 mesh) purchased from Sisco and purified products were recrystallized. ^1H NMR spectra were recorded on a Bruker AvanceSpectrospin 300 (300 MHz). All NMR samples were run in CDCl_3 and chemical shifts are expressed as δ relative to internal TMS. IR spectra were obtained on Perkin Elmer FT-IR spectrometer spectrum-2000 using potassium bromide pellets. ESI-MS mass spectra were recorded on waters LCT micro mass. The temperature of the reaction mixture was measured through a non-contact infrared thermometer (AZ, Mini Gun Type, Model 8868).

General procedure for the synthesis of benzimidazoles: In a 50 ml round bottom flask, a mixture of o-phenylenediamine (OPD) (1 mmol) and aldehydes(1 mmol) in polypropylene glycol 200 (5 ml) were mixed and stirred in the presence of zinc chloride catalyst (5 mol%) at 50°C for 2 h. The progress of reaction mixture was monitored by TLC. On completion of reaction, the reaction mixture was cooled in dry ice-acetone bath to precipitate the PPG 200 and extracted with ether (PPG being insoluble in ether). The reaction mixture was filtered in order to recover the catalyst and filtrate was washed with H_2O and dried. The crude product was purified by silica-gel column chromatography using 15% ethyl acetate as an eluent to yield the 2-arylbenzimidazoles. The recovered PPG can be reused for further reactions. All the known compounds were characterized by comparing their physical constant and spectral data (IR, ^1H NMR, LCMS and ^{13}C NMR).

RESULTS AND DISCUSSION

In continuation of our efforts on developing green methodologies for biologically active organic compounds, we reported here a ZnCl_2 catalysed procedure for the synthesis of benzimidazole derivatives in PPG at 50°C . Initially, a blank reaction was carried out using 1equiv. each of o-phenylenediamine and benzaldehyde. These were stirred at ambient temperature in ethanol for 12 h and only 65% of the expected product was obtained. The same reaction was then carried out using PPG 200 as the reaction medium under similar conditions. Surprisingly, a significant improvement was observed and the yield of product

was dramatically increased to 85% for 10 h. Further to improve the yield and also to explore the catalytic activity of $ZnCl_2$ the reaction was carried out with same amount of reactants in PPG (5 mL) we restirred at $50^\circ C$ in the presence of 2 mol% of $ZnCl_2$ for 5 h, a good improvement was observed and the reaction yield is 90% benzimidazole (scheme 1). With this optimistic result in hand, we further investigated the best reaction condition by using different amounts of $ZnCl_2$. An increase in the quantity of $ZnCl_2$ from 2 mol% to 5 mol%, not only decreased the reaction time from 5 h to 2 h but also increased the product yield from 90 to 92.

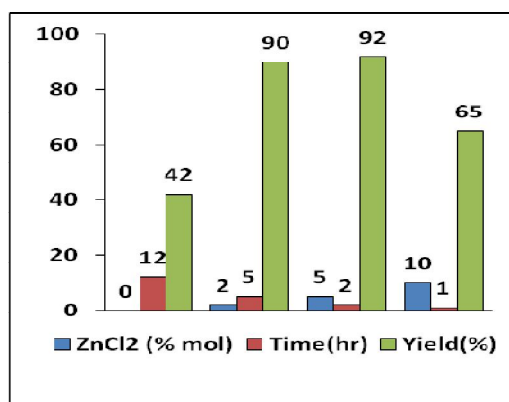
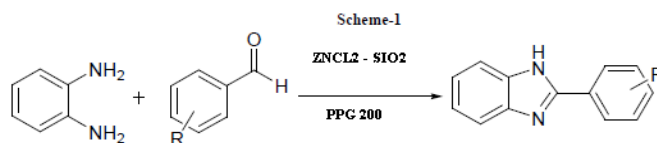
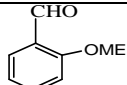
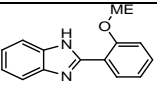
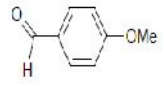
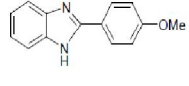
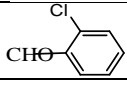
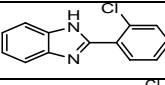
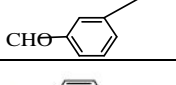
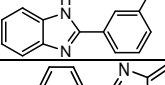
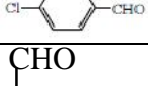
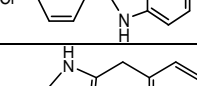
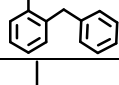
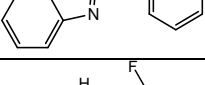
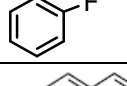
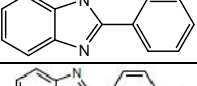
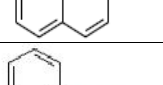
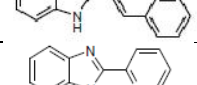
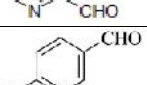
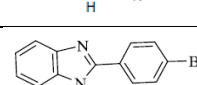
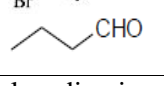
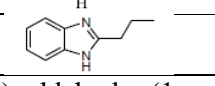
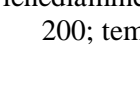
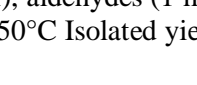


Figure 1. Catalytic activity evaluation for benzimidazoles. Reaction conditions: o-phenylenediamine (1 mmol), benzaldehyde(1 mmol); solvent PPG200 . temperature $50^\circ C$. Isolated yields.

Table 1. Synthesis of 2-phenyl benzimidazole derivatives by using $ZnCl_2$ -PPG 200 system.

Entry	Aldehyde	Product	Yield (%)
1			98
2			92
3			90
4			91
5			96
6			98
7			96

8			95
9			92
10			92
11			85
12			96
13			93
14			96
15			94
16			95
17			94
18			96

Reaction conditions: *o*-phenylenediamine (1 mmol), aldehydes (1 mmol), ZnCl₂ (5 mol%); solvent PPG 200; temperature 50°C Isolated yields.

Although the use of 10 mol% of ZnCl₂ permitted the reaction time to be decreased to 1h, the yield unexpectedly decreased to 65%. A possible explanation for the low product yields is that the starting material or the product may have been destroyed during the reaction when excess amount (10 mol%) of ZnCl₂ was used in the reaction. It appears that a concentration of 5 mol% of ZnCl₂ is the suitable choice for an optimum yield of benzimidazoles (figure 1). In order to study the generality of this procedure, the applicability of the PPG 200 with ZnCl₂ system was then examined for the reaction of a series of aromatic aldehydes with *o*-phenylenediamine under the optimized reaction conditions (table 1). As shown, a variety of substituted aromatic aldehydes, bearing either electron-donating or electron-withdrawing substituents, afforded the products in excellent yields and high purities. In addition, heterocyclic aldehydes could also be used for efficient preparation of various heterocyclic-benzimidazoles (table 1, entry 3 and 4). It was interesting to observe the remarkable stability of a variety of functional groups such as ether, nitro, hydroxyl, halides, and formyl under the reaction conditions. The nature of reaction media has an important role in the synthesis of benzimidazoles in the presence of ZnCl₂ (5 mol%). Almost all solvents afforded products in excellent yield with a variation in reaction time. Therefore we used only PPG 200 as a solvent because it is recyclable, non-toxic and thermally stable (figure 2)

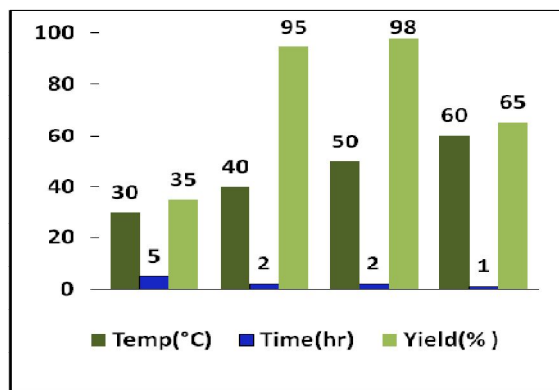


Figure 2: ZnCl₂ catalyze Benzimidazoles reaction in various solvents. Reaction conditions: o-phenylenediamine(1 mmol), benzaldehyde (1 mmol); solvent PPG 200; temperature 50°C. Isolated yields.

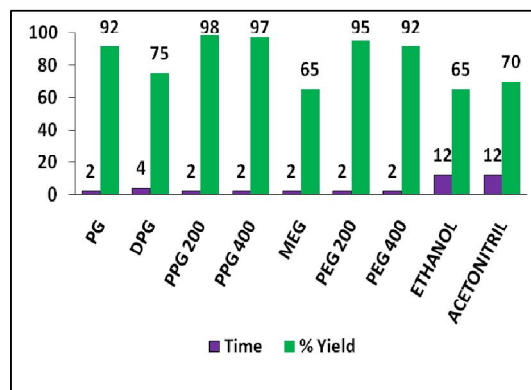


Figure 3: Effect of Temperature. Reaction conditions: o-phenylenediamine (1 mmol), benzaldehyde (1 mmol), ZnCl₂ (5 mol%); solvent PG 400; temperature 50°C. Isolated yields.

The effect of temperature was also studied. Faster reactions occurred on raising the temperature but the yield of product decreased at higher temperature possibly because one of the reactants (aldehydes) oxidizes at high temperature in presence of ZnCl₂ (figure 3). In order to prove that the use of PPG as solvent is also practical, it was recycled with minimum loss and decomposition. Since poly PPG is immiscible with solvent ether, the desired product may be extracted with it and remaining PPG phase may be used. The solvent phase was recycled with no change in reactivity for three cycles but approximately 5% weight loss of PPG was observed from cycle to cycle (figure 4). Overall this methodology offers the competitive advantages of recyclability of the solvents which could be used without further purification and without any additions. It also requires less loading of the catalyst and has broad substrate applicability with ease and improved yields. In addition low cost, recyclable solvent system and ready availability of catalyst, an environmentally benign procedure makes this methodology a useful contribution to the existing procedures available for the synthesis of benzimidazole derivatives.

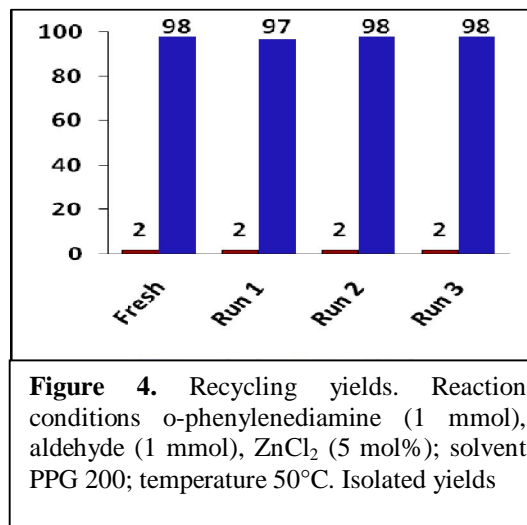


Figure 4: Recycling yields. Reaction conditions o-phenylenediamine (1 mmol), aldehyde (1 mmol), ZnCl₂ (5 mol%); solvent PPG 200; temperature 50°C. Isolated yields

APPLICATIONS

These methods involve use of solvent free method or use of recyclable organic solvents. The low cost, recyclable solvent system and ready availability of catalyst, an environmentally benign procedure makes this methodology, a useful contribution to the existing procedures available for the synthesis of benzimidazole derivatives.

CONCLUSIONS

In conclusion, the PPG has been employed as a novel, mild and highly efficient solvent system for the convenient preparation of benzimidazoles in excellent yields from o-phenylenediamine and a wide variety of aryl aldehydes using $ZnCl_2$ as catalyst. In addition low cost, recyclable solvent system and ready availability of catalyst, an environmentally benign procedure makes this methodology a useful contribution to the existing procedures available for the synthesis of benzimidazole derivatives.

REFERENCES

- [1] P.S.Rathee, R. Dhankar, S. Bhardwaj, M. Gupta, RakeshKumar, *Journal of Applied Pharmaceutical Science*, **2011**, 1(10), 140-142.
- [2] H.Nakano, T.Inoue, N.Kawasaki, H. Miyataka, H. Matsumoto, T. Taguchi, N. Inagaki, H.Nagai, T. Satoh, *Chem Pharm Bull*, 1999, 47(11), 1573-1578.
- [3] T.Fonseca, B. Gigante, M.M.Marques, T.L. Gilchrist, E.D. Clercq, *Bioorg. Med. Chem.*, **2004**, 12, 103-112.
- [4] G.N.Vazquez, L. Yopez, A.H. Campos, A. Tapia, F.H. Luis, R.Cedillo, J.Gonzalez, A.M.Fernandez, M.M. Grueiro, R. Castillo, *Bioorg. Med. Chem.*, **2003**, 11, 4615-4622.
- [5] B.Serafin, G. Borkowska, J. Głowczyk, I. Kowalska, S. Rump, *Pol J Pharmacol Pharm*, **1989**, 41(1), 89-96.
- [6] T.Bethke, D. Brunkhorst, H. von der Leyen, W. Meyer, R. Nigbur, H. Scholz, *Naunyn Schmiedebergs Arch Pharmaco*, **1988**, 337(5), 576-582.
- [7] F.R.Khan, A.J. Asnani, *International Journal of Research in Pharmaceutical and Biomedical Sciences*, **2011**, 2(2), 695-700.
- [8] M.H.Al-Douh, H.B. Sahib, H. Osman, S.A. Hamid, S.M. Salhimi. *Asian Pacific J Cancer Prev*, **2012**, 13, 4075-4079.
- [9] E.S.Lazer, M.R. Matteo, G.J. Possanza, *J Med Chem.*, **1987**, 30(4), 726-729.
- [10] S. Aydin, R. Beis, O.D. Can, *Pharmazie*, **2003**, 58(6), 405-408.
- [11] Z. Ateş-Alagöz, C Kuş, T. Coban, *J Enzyme Inhib Med Chem.*, **2005**, 20(4), 325-331.
- [12] Z. Kazimierzuk, J.A. Upcroft, P. Upcroft, A. Górska, B. Starościak, A. Laudy, *Acta Biochim Pol*, **2002**, 49(1), 185-195.
- [13] R. Vinodkumar, S.D. Vaidya, B.V. SivaKumar, U.N. Bhise, S.B. Bhirud, U.C Mashelkar, *ARKIVOC*, **2008**, xi (v), 37-49.
- [14] V.G. Pashinskiĭ, T.V. Romanova, N.A. Mukhina, L.V. Shkrabova, K.P. Tetenchuk, *Farmakol Toksikol.*, **1978**, 41(2), 196-199 (043).
- [15] R.A. Ng, J. Guan, V.C. Alford Jr, J.C. Lanter, G.F. Allan, T. Sbriscia, O. Linton, S.G. Lundeen, Z. Sui, *Bioorg Med Chem Lett*, **2007**, 17(3), 784-788.
- [16] B. Bhriġu, N. Siddiqui, D. Pathak, M.S. Alam, R. Ali, B. Azad, *Acta Poloniae Pharmaceutica-Drug Research*, **2012**, 69(1), 53-62.
- [17] S.Sajjadifar, S.A. Mirshokraie, N. Javaherneshan, O. Louie, *American Journal of Organic Chemistry*, **2012**, 2(2), 1-6.
- [18] K.F. Shelke, S.B. Sapkal, G.K. Kakade, P.V. Shinde, B.B. Shingate, M.S. Shingare, *Chin. Chem. Lett.*, **2009**, 20, 1453-1456
- [19] R.R Nagawade, D.B. Shinde, *Chem. Lett.*, **2006**, 17(4), 453-456.
- [20] P.P. Patila, M.B. Deshmukh, et al., *Der Pharma Chemica*, **2011**, 3(6), 599-605.
- [21] M. Forouzani, H.G. Bosra, *E-Journal of Chemistry*, **2012**, 9(3), 1064-1069.

- [22] D.T. Nannapaneni, A.V.S.S.S. Gupta, M.I. Reddy, R.C. Sarva, *J Young Pharm.*, **2010**,2(3),273–279.
- [23] H.M. Bachhav, S.B. Bhagat, V.N. Telvekar, *Tetrahedron Lett* **2011**, 52, 5697–5701.
- [24] G.M. Ziarani, A. Badieli, M. Hassanzadeh, *International Journal of Applied Biology and Pharmaceutical Technology*, 2011, 2(1), 48-54.
- [25] A.R. Momeni, S. Bagheri, *Iran. J Catalysis*, **2012**, 2(1), 31-35.
- [26] K.A. Shaikh, V.A. Patil, *Org. Commun*, **2012**, 5(1), 12-17.
- [27] K.P. Boroujeni, A. Zhianinasab, M. Jafarinasab, *J. Serb. Chem. Soc.*, **2012**, 77, 1–17.
- [28] V.D. Patil, G. Medha, M. Shramesha, J. Aarti, *Der Chemica Sinica*, **2010**, 1(2), 125-129.
- [29] F.K Behbahani, P. Ziaei, *Chemistry of Heterocyclic Compounds*, **2012**, 48(7), 1011-1017.
- [30] R.S.Joshi, P.G. Mandhane, S.K. Dabhade, C.H. Gill, *J. Chin. Chem. Soc.*, **2010**, 57, 1227-1231.
- [31] M. Kidwai, A. Jahan, D. Bhatnagar, *J. Chem. Sci.*, **2010**,122(4),607–612.
- [32] M.M. Heravi, N. Javanmardi, H.A Oskooie, B. Baghernejad, M. Heidari ,F.F. Bamoharram, *J. Chin. Chem. Soc.*, **2009**, 56,589-593.
- [33] N.Y. Sreedhar, M.R. Jayapal, K.S. Prasad, P.R. Prasad, *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, **2010**, 1(4), 480-485.
- [34] A.V. Narsaiah, R.S. Ghogare, D.O. Biradar, *Org. Commun.*, **2011**, 4(3), 75-81.