Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2017, 9(8):209-213

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Green and Efficient Synthesis of Benzimidazole Derivatives and their Antibacterial Screening

Chandrashekhar G Devkate[1*], Khandu D Warad[2], Mahendra B Bhalerao[2], Digambar D Gaikwad[3] and Mohammad Idrees M Siddique[4]

[1]Department of Chemistry, Indraraj Arts, Commerce and Science College Sillod, India
[2]Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, India
[3]Department of Chemistry, Govt. College of Arts and Science, Aurangabad, India
[4] Department of Chemistry, Government of Institute Science, Nagpur, India

---

ABSTRACT

*Here in we report a green and efficient synthesis of benzimidazoles and its derivatives, by the condensation of 1,2-phenylendiamine and orthoesters in presence of ionic liquid, 1-butylimidazolium bisulphate [Hbim][HSO_4] as a catalyst and water as solvent. The synthesis highlights a comparative study of conventional, ultrasound and microwave techniques. The products obtained in good to moderate yields with simple work up procedure. The compound **3c** was investigated in vitro against Gram +ve and Gram –ve bacteria at different concentrations and compared with standard drug ciprofloxacin.*

Keywords: Benzimidazoles; Ionic liquid; Microwave; Ultrasound; Antibacterial

---

INTRODUCTION

Benzimidazole is an important substructure found in a wide range of bioactive compounds and in pharmaceuticals [1,2]. They are the key structural intermediate in the synthesis of a variety of bioactive compounds [3,4]. These moieties serve as important intermediates in numerous organic reactions and used as important ligands for transition metals in various organic transformations [5,6]. Benzimidazole has evolved as an important heterocyclic system due to its presence in a wide range of bioactive compounds like antiparasitics, anticonvulsants, analgesics, antihistaminics, antiulcers, antihypertensives, antiviral, anticancers, antifungals, anti-inflammatory agents, proton pump inhibitors and anticoagulants [7-13]. Many synthetic methods have been developed and modified to get products of high yield, purity and of desired quality. But increasing concern with regard to the tight legislation on the maintainence of 'greenness' in the synthetic pathways and processes. Due to growing environmental concern, designing of straightforward and practical chemical syntheses of drugs and fine chemicals that satisfy economic criteria is a major challenge [14]. Therefore, in an endeavor towards the development of greener synthetic protocols for the Synthesis of benzimidazole derivatives and the use of ultrasound as efficient and attractive methodology [15,16]. Ionic liquids (ILs) as 'green' solvents in organic synthetic processes has gained considerable importance due to their solvating ability, negligible vapour pressure, high thermal stability, low melting points, good solvating capabilities, wide electrochemical window, inflammability, intrinsic ionic conductivities, easy recyclability and reusability [17-21]. And another non-conventional method which is MAOS where use of ionic liquids as solvent, co-solvent and/or catalyst, since they are "eco-friend solvents" [22,23] and ionic in nature, allows a very effective

coupling with microwave energy [24]. Compared with traditional methods, these reactions are more convenient and advantageous.

EXPERIMENTAL SECTION

General Considerations

All reagents and solvents purchased from commercial sources were used as received. The ionic liquids was prepared by reported procedure and used. All reactions were carried out in oven-dried glassware and were magnetically stirred. FTIR spectra were taken on FT Infra-Red Spectrophotometer Model RZX (Perkin Elmer) and ^{1}H and ^{13}C spectra were taken on bruker AVANCE II 400 MHz spectrometer with TMS as internal standard $CDCl_3$ / DMSO as solvent. ESI-Mass spectral data were recorded on Q-TOF Micro Waters (ESI-MS) Spectrometer.

General Procedure for the Screening of Ionic Liquids

Screening of ionic liquids for the synthesis of benzimidazoles, various reaction conditions have been investigated in the reaction of 1,2-phenylendiamine 1 and 1,1,1-trimethoxyethane 2c as a model reaction (Scheme 1). We examined the effect of different ionic liquids such as N-butyl imidazolium [Hbim] and N,N-dibutyl imidazolium [bbim], the salts with varying basicity like [Hbim][HCOO], [Hbim][CH_3COO], [Hbim][TOS], [Hbim][HSO_4], [bbim][HSO_4], [bbim][CH_3COO], [bbim][TOS] and [bbim][HCOO] were synthesized and used in a model reaction which was carried out by conventional method at 80°C. The results were summarized in Table 1. The excellent yield was isolated from all the imidazolium based ionic liquids which were screened but [Hbim][HSO_4] and [bbim][HSO_4] afforded the best yield for the reaction (Table 1, entry 4,5). And we have chosen [Hbim][HSO_4] for our further synthesis of benzimidazoles derivatives.

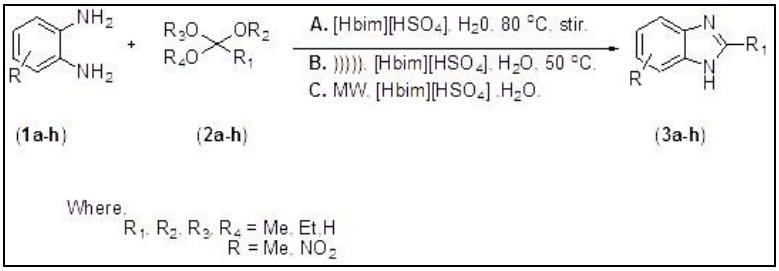
Table 1: Screening of ionic liquids to search a suitable medium for the synthesis of benzimidazoles (3c)[a]

Entry	Ionic liquids	Time (min)	Yield[b]%
1	[Hbim][HCOO]	30	50
2	[Hbim][CH_3COO]	30	55
3	[Hbim][TOS]	30	60
4	[Hbim][HSO_4]	30	70
5	[bbim][HSO_4]	30	65
6	[bbim][CH_3COO]	30	53
7	[bbim][TOS]	30	58
8	[bbim][HCOO]	30	53

[a]**Reaction Conditions**

A mixture of 1,2-phenylendiamine 1 (1.0 mmol) and 1,1,1-trimethoxyethane 2c (1.1 mmol) was dissolved in ionic liquids (1.1) and water (5ml) and stirred at 80°C for 30 min.

[b]Isolated yields.



Scheme 1: Synthesis of substituted benzimidazoles (3a-h) using [Hbim][HSO_4]

General Procedure for the Synthesis of Benzimidazoles (3a-3h)

Method (A): By conventional method:

A mixture of 1,2-phenylendiamine 1 (1.0 mmol) and 1,1,1-trimethoxyethane 2c (1.1 mmol) was dissolved in 100 mL round bottom flask to that [Hbim][HSO_4] (1.1 mmol) as a catalyst and water (5 ml) as a solvent was added. Reaction mixture was stirred for 20-30 min. at 80°C. Progress of the reaction was monitored with the help of TLC. After completion of the reaction, the reaction mixture was diluted with water (20-30 ml) and the separated product was filtered and was washed thoroughly with water and dried. The aqueous layer consisting of the IL was subjected to distillation at 80°C to remove the water and leaving behind the IL here there was recovery for ([Hbim][HSO_4]

90%), thus ILs was recycled and used. The same procedure was repeated for two times. The product thus obtained was pure enough, got single spot on TLC. Then product was crystallized using (1:1) DMF-Ethanol. The procedure was followed to prepare other analogs of this series (Tables 2 and 3). As the products are known compounds were characterized by comparison of their spectral data (IR, Mass, ^{1}H-NMR and ^{13}C-NMR) and physical properties with those reported in literature.

Table 2: Effect of mole ratio of ionic liquid on yield of 3c

Entry	Moles ratio of IL (mmol%)	[Hbim][HSO_4] Yield (%)		
		Conventional Method	Ultrasound Method	Microwave Method
1	2	5	8	3
2	5	12	15	10
3	10	40	45	38
4	15	70	75	68
5	20	90	94	85
6	25	82	85	78

Method (B): By ultrasound method:

A mixture of 1,2-phenylendiamine 1 (1.0 mmol) and 1,1,1-trimethoxyethane 2c (1.1 mmol) was dissolved in 100 mL round bottom flask to that [Hbim][HSO_4] (1.1 mmol) as a catalyst and water (5 ml) as a solvent was added. Reaction mixture was immersed into the ultrasonic water bath, where the surface of the reactants is slightly lower than the level of the water, and irradiated at 40% of the power of the ultrasonic bath at 50°C for 10-15 min. Progress of the reaction was monitored with the help of TLC. After completion of the reaction the process of recyclation of Ionic liquid, crystallization and characterization was done as given in (method A).

Method (C): By microwave method:

A mixture of 1,2-phenylendiamine 1(1.0 mmol) and 1,1,1-trimethoxyethane 2c (1.1 mmol) was dissolved in 100 mL round bottom flask to that [Hbim][HSO_4] (1.1 mmol) as a catalyst and water (5 ml) as a solvent was added. Reaction mixture was exposed in a microwave oven of 210 W and irradiated for a period of 30 sec. at a time. After each irradiation the reaction mixture was removed from the microwave for shaking. The total time of microwave irradiation was 2-4 min. Progress of the reaction was monitored with the help of TLC. After completion of the reaction the process of recyclation of Ionic liquid, crystallization and characterization was done as given in (method A).

Spectral Data for Representative Benzimidazole

Compound 3c: white solid; mp 176 -178°C. FTIR Model RZX (Perkin Elmer) cm^{-1}: 3060, 1555, 1271,735. ^{1}H-NMR (400 MHz, DMSO-d_6, d ppm): δ, 2.52 (s, CH_3) δ, 7.09-7.11 (m, 2H, Ar H), 7.43-7.46 (m, 2H, Ar H), 10.89 (s, 1H, -NH); ^{13}C-NMR (400 MHz, DMSO-d_6, d ppm): δ, 14.51, 114.07, 121.1, 138.73, 151.11. MS (EI): m/z (%) =133.06 [M^+].

Antibacterial Activity

The novel synthesized heterocyclic compound 3c was screened for *in vitro* antimicrobial activity using agar disc-diffusion method against two gram positive bacterial strains, *Staphylococcus aureus* and *Bacillus subtilis* and two gram negative strains, *Escherichia coli* and *Pseudomonas aeruginosa* [25,26]. Ciprofloxacin was used as standard drug.

General Procedure: Determination of Zone of Inhibition by Agar Disc-Diffusion Method

Test solutions were prepared with known weight of compound in DMSO and half diluted suitably to give the resultant concentration of 125-1000 µg/mL. Whatmann no. 1 sterile filter paper discs (6 mm) were impregnated with solution and allowed to dry at room temperature.

In vitro antibacterial activity was determined by using Mueller Hinton Agar obtained from Himedia Ltd., Mumbai. Petri plates were prepared by pouring 20 mL of Mueller Hinton Agar for bacteria containing microbial culture was allowed to solidify. 24 hrs old cultures were used to get 10^8 suspensions. This suspension of 4 pathogenic cultures was spread on Muller Hinton Agar plates by sterile cotton swabs. The impregnated discs were then kept on these plates and were incubated at 37°C for 24 h (bacteria) and after incubation zone of inhibition was measured in mm as diameter in four directions and expressed as mean. The results were compared against Ciprofloxacin as a standard drug and are reported in the following (Table 4). Data obtained from antibacterial assessment are furnished in Table 4 indicates that the test compound 3d showed antibacterial activity against Gram positive bacteria, *S. aureus* and *B.*

subtilis it moderate activity against *S. aureus* no activity against *B. subtilis.* In case of gram negative bacteria, 3c showed moderate activity against *E. coli* and it is inactive against *P. aeruginosa* at all 4 concentrations. On the basis of data it is clear that 2-methylbenzimidazole and its derivatives possesses moderate antibacterial activity.

Table 3: Synthesis of substituted benzimidazoles (3a-h) using [Hbim][HSO_4]

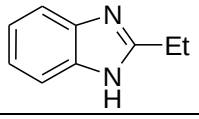
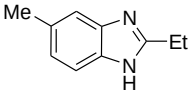
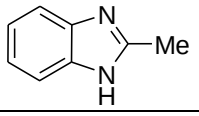
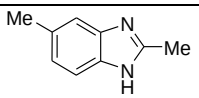
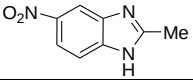
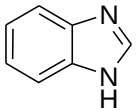
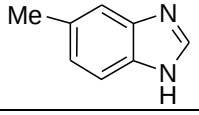
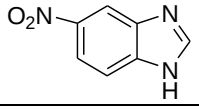
Comp.	Orthoester	Product	m.p oC	Conventional Method		Ultrasound Method		Microwave Method	
				Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
3a	$EtC(OEt)_3$		166 - 168	28	68	15	86	3	70
3b	$EtC(OEt)_3$		165 - 167	25	72	13	89	3	72
3c	$MeC(OMe)_3$		176 - 178	30	70	18	94	2.5	74
3d	$MeC(OMe)_3$		198 - 200	23	74	10	90	3	68
3e	$MeC(OMe)_3$		225 - 227	18	77	8	92	2.5	80
3f	$HC(OEt)_3$		170 - 172	30	64	15	90	4	78
3g	$HC(OEt)_3$		108 – 110	25	68	12	78	3	73
3h	$HC(OEt)_3$		208 - 210	20	75	10	88	2	82

Table 4: Antibacterial activity of 3c

Sr. No.	Conc µg/mL	Zone of inhibition in mm							
		Gram +ve				Gram -ve			
		3c							
		Pathogen – *Staphylococcus aureus*		Pathogen – *Bacillus subtilis*		Pathogen – *Escherichia coli*		Pathogen – *Pseudomonas aeruginosa*	
		Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2
1	125	12	10	-	-	7	7	-	-
2	250	16	16	-	-	8	8	-	-
3	500	21	23	-	-	12	12	-	-
4	1000	27	28	-	-	18	19	-	-
Standard Ciprofloxacin									
1	125	31	31	27	27	26	26	27	27
2	250	35	36	29	29	28	28	32	32
3	500	40	41	30	31	29	31	36	34
4	1000	44	45	32	33	30	33	38	39

RESULTS AND DISCUSSION

The present method involves condensation of 1,2-phenylendiamine 1 and orthoester (2a-2h) was chosen to obtain benzimidazoles. Following the green chemistry approach we decided to use eco-friendly, non-hazardous ionic liquids as catalyst and water as solvent. Initially we have screened different imidazolium based ionic liquids were [Hbim][HSO_4] and [bbim][HSO_4] afforded the best yield for the reaction (Table 1, entry 4,5). And we have chosen [Hbim][HSO_4] for our further synthesis benzimidazoles derivatives. After this, the reaction was performed in the presence of 02, 05, 10, 15, 20 and 25 (mol%) of (Table 2) with three different methods (conventional, ultrasound, microwave). In all cases, the experimental result shows that the reaction times are shorter and the yields of the products are higher under non-conventional methods as compared to conventional method. The best results were obtained using 20 mol of the catalyst (Table 2, entry 5). Then the further synthesis of benzimidazoles derivatives using [Hbim][HSO_4] (20 mol%) of catalyst and water (5 ml) as a solvent, all the reaction was carried out by three different method (conventional, ultrasound, microwave) and the result obtained are shown (Table 3). The compound 3c was screened for *in vitro* antibacterial activity using agar disc-diffusion method against two gram positive bacterial strains, *Staphylococcus aureus* and *Bacillus subtilis* and two gram negative strains, *Escherichia coli* and *Pseudomonas aeruginosa*. Ciprofloxacin was used as standard drug and the data obtained from antibacterial assessment are furnished in Table 4.

CONCLUSION

In conclusion, we report a comparative study of conventional, ultrasound and microwave techniques for the synthesis of benzimidazoles and its derivatives, using 1-butylimidazolium bisulphate [Hbim][HSO_4] as a catalyst and water as solvent. Where non-conventional methods are found to be very clean and require shorter reaction time and the products obtained in good to moderate yields with simple work up procedure. Antibacterial screening of 3c compound was found to possess moderate activity against selected strains of bacteria also found inactive for *B.subtilis* and *P.aeruginosa* and rest of synthesized will be assessed in future study.

REFERENCES

[1] M Zhou; YJ Eun; AG Ilia; DB Weibel. *Med Chem Lett*. **2013**, 4, 880-885.
[2] YB Xu; L Yang; GF Wang; XK Tong; YJ Wang; Y Yu; JF Jing; CL Feng; PL He; W Lu; W Tang; JP Zuo. *Antiviral Res*. **2014**, 107, 6-15.
[3] M Gaba; S Singh; C Mohan. *Eur J Med Chem*. **2014**, 76, 494-505.
[4] Y Gong; SS Karakaya; X Guo; P Zheng; B Gold; Y Ma; D Little; J Roberts; T Warrier; X Jiang; M Pingle; CF Nathan; G Liu. *Eur J Med Chem*. **2014**, 75, 336-353.
[5] Y Bai; J Lu; Z Shi; B Yang. *Synlett*. **2001**, 544-546.
[6] M Kose; V Mckee. *Polyhedron*. **2014**, 75, 30-39.
[7] QA McKellar; EW Scott. *J Vet Pharmacol Ther*. **1990**, 13, 223.
[8] AA Spasov; IN Yozhitsa; LI Bugaeva; VA Anisimova. *Pharm Chem J*. **1999**, 33, 232.
[9] JF Rossignol; H Maisonneuve. *Ann Trop Med Parasitol*. **1984**, 78, 135.
[10] A Patil; S Ganguly; S Surana. *Rasayan J Chem*. **2008**, 1, 447.
[11] AK Dubey; PK Sanyal. *Online Vet J*. **2010**, 5, 63.
[12] M Boiani; M Gonzalez. *Mini Rev Med Chem*. **2005**, 5, 409.
[13] B Narasimhan; D Sharma; P Kumar. *Med Chem Res*. **2012**, 21, 269.
[14] A Chanda; VV Fokin. *Chem Rev*. **2009,** 109, 725.
[15] MR Nabid; SJT Rezaei; R Ghahremanzadeh; A Bazgir. *Ultraso Sonochem*. **2010,** 17, 159.
[16] JT Li; JF Han; JH Yang; TS Li. *Ultrason Sonochem*. **2003**, 10, 119.
[17] J Fuller; AC Breda; RT Carlin. *J Electrochem Soc*. **1997**, 144, 67.
[18] W Peter; K Wilhelm. *Angew Chem Int Ed.* **2000**, 39, 3772.
[19] P Wasserscheid, T Welton. *Ionic Liquids Synthesis*. **2003**.
[20] M Smiglak; A Metlen; RD Rogers. *Acc Chem Res.* **2007**, 40, 1182.
[21] MJ Earle; KR Seddon, *Pure Appl Chem*. **2000**, 72, 1391.
[22] H Zhao; V Malhotra. *Aldrichimica Acta*. **2002**, 35, 75-83.
[23] PJ Scammells; JA Scott; RD Singer. *Aust J Chem.* **2005**, 158, 155-169.
[24] J Karkkainen; J Asikkala; RS Laitinen; MKZ Lajunen. *Naturforsch B.* **2004**, 59, 763-770.
[25] DN Fish. *Am J Health Sys Pharm.* **2002**, 59, 13.
[26] RJ Belland. *Cell Microbial*. **2004**, 6,117.