Research Article

Green Synthesis of Some Novel Substituted and Unsubstituted Benzimidazole Derivatives by Using Microwave Energy

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Accepted on: 30-04-2014; **Finalized on:** 30-06-2014.

ABSTRACT

The development of simple, efficient and general synthetic method for biological active compounds is one of the major challenges in organic synthesis. The importance of benzimidazole compound arises, because they are found in many biologically active compounds. Recently, several methods have been developed, for the synthesis of benzimidazole derivative like use of catalyst such as sulphur, ultrasonic, Lewis acids like pyridinium-p-toluenesulfonate, ionic liquids like polyaniline-sulfate and Zeolite. But, all of this reported method has several disadvantages such as, use of organic solvents, harsh reaction conditions, prolonged reaction times, use of expensive reagents. To overcome all these disadvantages here we report a practical, inexpensive and green method for the synthesis of benzimidazole derivatives under solvent free-condition.This growth of green chemistry holds significant potential for a reduction of the byproduct & waste production and a lowering of the energy costs. The one pot condensation of o-phenylenediamine 1 with substituted/ unsubstituted thiourea 2 under microwave irradiation in solvent-free condition gave substituted/ unsubstituted benzimidazole-2-thione derivative 3a-g with excellent yield is described here.

Keywords: One pot condensation, bezaimidazole-2-thiones, o-phenylenediamine, solvent-free, Green synthesis, microwave irradiation.

INTRODUCTION

The heterocyclic compound Benzimidazole derivatives are formed by the fusion of benzene and imidazole ring which containing nitrogen, oxygen sulphur. A per usual literature reveals that among many pesticidal, nitrogen and sulphur heterocyclic, strong feature for their activities is the presence of NCS linkage. The imidazole core is a common moiety in a large number of natural products and pharmacologically active compounds. On the basis of various literature surveys Imidazole derivatives shows various pharmacological activities like antifungal[1], antibacterial activity[2], anti inflammatory activity[3], antitubercular[4] activity, anti depressant activity[5], anticancer activity[6], antiviral activity[7].

Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications, they are remarkably effective compounds with respect to their inhibitory activity as well as their selectivity.In view of importance benzimidazole as a chemotherapeutic agent[8,9], and development of a facile, efficient and environmentally benign method to synthesize this heterocyclic compound would be great value.

In addition, thiourea derivatives which are used in synthesis of benzimidazole-2-thione derivative are also associated with a wide range of biological activities such anticancer[10], antimicrobial[11,12] antibacterial[13], antifungal[14], antimalarial[15] and antituberculosis[16]

Benzimidazole derivatives known to possess excellent biological activity like antiulcers[17], antihypertensives[18], antihistaminics[19], antitubercular[20], antiasthmatic[21], anti-diabetic[21] and antiprotozoal[22]. Further mercapto benzimidazole affects CNS and some of them are found even more effective than morphine. This observation prompted us to develop an environmentally benign protocol for synthesis of some substituted / unsubstituted benzimidazole-2-thiones which possess antibacterial[23], antifungal[23], anticancer[24] and antiviral[25] activities.

The synthesis of benzimidazole commonly involves the cyclo-phenylene diamine with substituted / unsubstituted thiourea or urethanes by refluxing in methanol or pyridine. All these method have some disadvantage like long reaction period, low yield and use of toxic organic solvents which pollute our environment.

The solvent free reaction or dry media techniques under microwave irradiation are one of the main fields of our research. Under microwave irradiation encouraged by above reports and as part of our research programme for development of eco-friendly synthetic protocol for biologically active compounds[26] as well as in pursuing of our work on new solvent-free cyclisation process we developed a regioselective, novel, solvent free, microwave activated synthesis of hitherto unknown Benzimidazol-2-thione (Scheme 1). The reaction time, yield, and ^{1}HNMR spectra are summarized in Table-1 and Table-2.

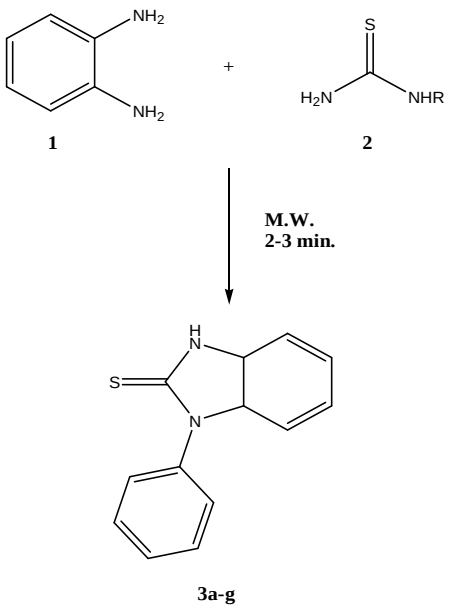
The reaction were carried out by mixing of o-phenylenediamine with N,N' substituted / unsubstituted thiourea in a beaker and the mixture was heated in household microwave oven, operating at medium power

(600W) for 2-3 min. Reaction mixture was cooled at room temperature and extracted with little amount of CH3CN to afford the substituted / unsubstituted bezaimidazole-2-thione derivative.

MATERIALS AND METHODS

Melting points were determined by open glass capillary method and are uncorrected. All chemicals used were reagent grade and were used as received. A Laboratory Microwave Oven (Model BP 310/50) operating at 2450 MHz and power output of 600 W was used for all the experiments. The completion of reactions was monitored by TLC (Merk silica gel). IR spectra were recorded on a Shimadzu FTIR-420 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400°C on a Bruker AVANCE DPX (400 MHz) FT spectrometer in $CDCl_3$ using TMS as an internal reference (chemical shift in δ, ppm). Mass spectra were recorded on JEOL SX-303 (FAB) mass spectrophotometer at 70ev. Elemental analyses were carried out using a Coleman automatic C, H, N analyser. The yield and melting point are given in **Table-1.**

Scheme-1



Microwave assisted synthesis of substituted/ unsubstituted bezaimidazole-2-thione 3_{a-g}

o-Phenylenediamine (0.001 mol) and N, N' substituted / unsubstituted thiourea (thiourea, phenylthiourea, o-tolyl thiourea, p--tolyl thiourea, benzyl thiourea, naphtyl thiourea, allyl thiourea) (0.001 mol) were mixed in a beaker thoroughly and the mixture was heated in household microwave oven, operating at medium power (600W) for the specified period (2-3 min) given in **Table-1**.

Thermal synthesis of substituted/ unsubstituted bezaimidazole-2-thione 3_{a-g}

o-Phenylenediamine (0.001 mol) and N, N' substituted / unsubstituted thiourea (thiourea, phenylthiourea, o-tolyl thiourea, p--tolyl thiourea, benzyl thiourea, naphtyl thiourea, allyl thiourea) (0.001 mol) were first dissolved in methanol. Then reaction mixture was refluxed on water bath at the time specified in **Table -1.**

RESULTS AND DISCUSSION

Microwave assisted synthesis of substituted/ unsubstituted bezaimidazole-2-thione 3_{a-g}

The completion of reaction was checked by TLC at every 30 sec. and after completion of reaction. The reaction-mixture was allowed to attain room temperature, then reaction-mixture was eluted CH_3CN with. The elute was evaporated to dryness under reduced pressure to obtain the crude product 3 $_{a-g.}$

Thermal synthesis of substituted/ unsubstituted bezaimidazole-2-thione 3_{a-g}

The completion of reaction was checked by TLC at every 30 sec. And after completion of reaction, the reaction-mixture was allowed to attain room temperature, then reaction-mixture was eluted CH_3CN with. The elute was evaporated to dryness under reduced pressure to obtain the crude product 3 $_{a-g.}$

Table 1: Melting point and Yield of Compound 3_{a-g}

Compound	R	Time		Yield (%)		M. P. (°C)
		MWI (min)	Thermal (hour)	MWI	Thermal	
3a	H	2	5	83	35	286
3b	$-C_6H_5$	3	4	85	32	276
3c	Allyl	3	5	88	33	308
3d	Naphthyl	2	5	90	34	298
3e	O-tollyl	3	4	89	33	312
3f	p- tollyl	3	4	92	35	285
3g	Benzyl	3	6	90	36	305

Table 2: Physical and ^{1}HNMR Spectra data of Compound 3_{a-g}

Compound	Mol. Formula	IR Spectra (KBr, υ.cm^{-1})	1 H-NMR ($CDCl_3$, δ, ppm)	Elemental Analysis	MS (EI, *m/z* (M^+)
3a	$C_7H_8N_2S$	1750	5.80-5.90 (m, 4H), 3.51(q,2H), 13.07 (s,2H, NH exchangeable with D2O)	C, 55.23; H, 5.30; N, 18.40; S, 21.07	52.041
3b	$C_{13}H_{12}N_2S$	1750	6.43-7.04 (m, 5H), 5.8-5.90 (m, 4H, Ar-H), 3.51(q, 2H), 13.07 (s, 1H, NH exchangeable with D2O).	C, 68.39; H, 5.30; N, 12.27; S, 14.04	228.072
3c	$C_{10}H_{12}N_2S$	1750	5.8-5.90 (m, 4H, Ar-H), 4.12 (d.2H,-CH_{2-}), 5.15-5.83(d, 3H), 3.51(q, 2H), 13.07 (s, 2H, NH exchangeable with D2O).	C, 62.46; H, 6.29; N, 14.57; S, 16.68	192.072
3d	$C_{17}H_{14}N_2S$	1750	5.8-5.90 (m, 4H, Ar-H), 4.12 (d.2H,-CH_{2-}), 6.76-7.55 (m, 7HAr-H), 3.51(q, 2H), 13.07 (s, 2H, NH exchangeable with D2O).	C, 73.35; H, 5.07; N, 10.06; S, 11.52	278.088
3e	$C_{14}H_{14}N_2S$	1750	5.8-5.90 (m, 4H,Ar-H),2.35 (s,3H,-CH_{3-}), 3.51(q,2H), 6.31-6.85 (m,4h,Ar-H),13.07 (s,2H, NH exchangeable with D2O).	C, 69.39; H, 5.82; N, 11.56; S, 13.23	242.088
3f	$C_{14}H_{14}N_2S$	1750	5.8-5.90 (m, 4H,Ar-H),2.35 (s,3H,-CH_{3-}), 3.51(q,2H), 6.31-6.85 (m,4h,Ar-H),13.07 (s,2H, NH exchangeable with D2O).	C, 69.39; H, 5.82; N, 11.56; S, 13.23	242.088
3g	$C_{14}H_{14}N_2S$	1750	5.8-5.90 (m, 4H,Ar-H),4.17 (d,2H,-CH_{2-}), 3.51(q,2H), 7.06-7.14(m,4h,Ar-H),13.07 (s,2H, NH exchangeable with D2O).	C, 69.39; H, 5.82; N, 11.56; S, 13.23	242.088

CONCLUSION

In the recent year microwave assisted organic reaction has emerged as new tool in organic synthesis and this is considered as an important approach toward green chemistry. This growth of green chemistry holds significant potential for a reduction of the by product & waste production and a lowering of the energy costs. So as part of our research programme for development of eco-friendly synthetic protocol for biologically active compounds as well as in pursuing of our work on new solvent-free cyclisation process we developed a regioselective, novel, solvent free, microwave assisted synthesis of hitherto unknown Benzimidazol-2-thione derivative which possess antimicrobial activities like antibacterial, antiviral and antifungal activities etc. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic imidazole nucleus. Although several method are available for synthesis of benzimidazole but all these method have some disadvantage like long reaction period, low yield and use of toxic organic solvents which pollute our environment.

Acknowledgement: The authors would like to express their gratitude and thanks to Department of Chemistry, DIT, and School of Engineering (Part of AMITY Education Group) Greater Noida for necessary facilities to carry out this research work and RSIC, CDRI Luck now for spectral analysis.

REFERENCES

1. Shingalapur R V, Hosamani KM, Keri RS, Synthesis and evaluation of in vitro anti-microbial and anti-tubercular activity of 2-styryl benzimidazoles, European Journal of Medicinal Chemistry,44, 2009, 4244–4248.
2. Sharma D, Narasimhan B, Kumar P, Judge V, Narang R, De Clercq E, Balzarini J, Synthesis, antimicrobial and antiviral evaluation of substituted imidazole derivatives, European Journal of Medicinal Chemistry, 44, 2009, 2347–2353.
3. Puratchikodya A and Doble M, Antinociceptive and anti-inflammatory activities and QSAR studies on 2-substituted-4, 5-diphenyl-1H-imidazoles & Medicinal Chemistry,15, 2007, 1083–1090.
4. Gupta P, Hameed S, Jain S, Ring-substituted imidazole as a new class of anti-tuberculosis agents, European Journal of Medicinal Chemistry, 39, 2004, 805–814.
5. Hadizadeh F, Hosseinzadeh H, Sadat Motamed-Shariaty, Seifi M and Kazemi S, Synthesis and Antidepressant Activity of N-Substituted Imidazole-5-Carboxamides in Forced Swimming Test Model, Iranian Journal of Pharmaceutical Research, 7(1),2008, 29-33.
6. Refaat H.M., Synthesis and anticancer activity of some novel 2-substituted benzimidazole derivatives, European Journal of Medicinal Chemistry, 45, 2010, 2949-2956.
7. Tonelli M, Simone M, Tasso B, Novelli F, Boido V, Antiviral activity of benzimidazole derivatives. II. Antiviral activity of 2-phenylbenzimidazole derivatives, Bioorganic & Medicinal Chemistry, 18, 2010, 2937–2953.
8. Preston PN, Synthesis, reactions, and spectroscopic properties of benzimidazoles, Chem. Rev., 74, 1974, 279.
9. Sharma S and Abuzar S, The benzimidazole anthelmintics chemistry and biological activity, Prog. Drug. Res., 27, 1983, 85-161.
10. Saeed S, Rashid S, Jones PG, Ali M, Hussain R, Synthesis, characterization and biological evaluation of some thiourea derivatives bearing benzothiazole moiety as potential antimicrobial and anticancer agents, European Journal of Medicinal Chemistry. 2010, 1323-1331.

11. Isab AA, Nawaz S, Saleem M, Altaf M, Mehboob MM, Ahmad A, Evans. HS Synthesis, characterization and antimicrobial studies of mixed ligand silver (I) complexes of thiourea and triphenylphosphine, Polyhedron. 2010, 1251-1256.
12. Saeed A, Shaheen U, Hameed A, Naqvi SZH, Synthesis, characterization and antimicrobial studies of some new 1-(fluorobenzoyl)-3-fluorophenyl) thioureas. Journal of Fluorine Chemistry. 2009, 1028-1034.
13. Rauf MK, Din I, Badshah A, Gielen M, Ebishara M, Vos D, Ahmed S, Synthesis, structural characterization and in vitro cytotoxicity and anti-bacterial activity of some copper(I) complexes with N,N'-disubstituted thioureas,Journal of Inorganic Biochemistry. 2009, 1135-1144.
14. Campo R, Criado JJ, Gheorghe R, González FJ, Hermosa MR, Sanz F, Manzano JL Monte, E, Fernandez ER, N-benzoyl-N'-alkylthioureas and their complexes with Ni(II), Co(III) and Pt(II) – crystal structure of 3-benzoyl-1-butyl-1-methyl-thiourea: activity against fungi and yeast. 2004.
15. Solomon VR, Haq W, Smilkstein M, Srivastava K, Puri SK, Katti SB, 4-aminoquinolone derived antimalarials: Synthesis, antiplasmodial activity and heme polymerization inhibition studies. European Journal of Medicinal Chemistry. 2010, 4990-4996.
16. Karakuş S, and Rollas S, Synthesis and antituberculosis activity of new N-phenyl-N'-[4-(5-alkyl/arylamino-1, 3, 4-thiadiazole-2-yl) phenyl] thioureas. I1 farmaco. 2002, 577-581.
17. Scott LJ, Dunn CJ, Mallarkey G, Sharpe M, Esomeprazole: A Review of its Use in the Management of Acid-Related Disorders, Drugs, 62, 2002, 1503.
18. Spasov AA, Yozhitsa IN, Bugaeva LI, Anisimova VA, Benzimidazole derivatives: Spectrum of pharmacological activity and toxicological properties (a review), Pharm. Chem. Journal, 33, 1999, 232.
19. Kim JS, Gatto B, Yu C, Liu A, Liu LF, LaVoie EJ, Substituted 2,5'-Bi-1H-benzimidazoles:Topoisomerase I inhibition and cytotoxicity, J. Med. Chem. 39, 1996, 992.
20. Shaikh and Patil, 17 Org. Commun., 51, 2012, 12-17
21. Shingalapur RV, Hosamani KM, Keri RS, Synthesis and evaluation of in vitro anti-microbial and anti-tubercular activity of 2-styryl benzimidazoles, Eur. J. Med. Chem., 44, 2009, 4244-4248.
22. Vinod kumar R, Vaidya SD, Siva Kumar BV, Bhise UN, Bhirud SB, Mashelka UC, Synthesis, anti-bacterial, anti-asthmatic and anti-diabetic activities of novel N-substituted-2-(4-phenylethynyl-phenyl)-1H-benzimidazoles and N-substituted 2[4-(4,4-dimethyl-thiochroman-6-ylethynyl)-phenyl)-1H-benzimidazoles, Eur. J. Med. Chem., 43, 2008, 986-995.
23. Navarrete-Vázquez G, Rojano-Vilchis MM, Yépez-Mulia L, Meléndez V, Gerena L, Hernández-Campos A, Castillo R, Hernandez Luis F, Synthesis and antiprotozoal activity of some 2-(trifluor-1H-benzimidazole bioisosteres, Eur. J. Med. Chem., 41, 2006, 135-141.
24. Sharma S, Gangal S, Rauf A, Convenient one-pot synthesis of novel 2-substituted benzimidazoles, tetrahydrobenzimidazoles and imidazole and evaluation of their in vitro antibacterial and antifungal activities, Eur. J. Med. Chem.,44, 2009, 1751-1757.
25. Refaat HM, Synthesis and anticancer activity of some novel 2-substituted benzimidazole derivatives. Eur. J. Med. Chem., 45, 2010, 2949-2956.
26. Roth T, Morningstar ML, Boyer PL, Hughes SH, Buckheit RWJ, Michejda CJ, Synthesis and Biological Activity of Novel Non nucleoside Inhibitors of HIV-1 Reverse Transcriptase. 2-Aryl-Substituted Benzimidazoles, J. Med. Chem., 40, 1997, 4199.
27. Paul AA, Pauld J, Synthesis of CBI-PDE-I-dimer, the benzannelated analogue of CC-1065, J. Org. Chem., 57, 1992, 6239.

Source of Support: Nil, **Conflict of Interest:** None.