RASĀYAN *J. Chem.*
Vol. 8 | No.2 |213 -217 | April - June | 2015
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

ONE POT SYNTHESIS OF SUBSTITUTED BENZIMIDAZOLE DERIVATIVES AND THEIR CHARCTERIZATION

S.R. Rithe, R. S. Jagtap and S.S. Ubarhande
P.G.Department of Chemistry, Shri Shivaji Science College, Amravti-66604
*E-mail:shri_orgchem@rediffmail.com

ABSTRACT
Benzimidazole derivatives plays important role in medical field with so many pharmacological activities such as antimicrobial ,antiviral ,antidiabetic ,anticancer ,activity. Various2-substituted benzimidazole derivatives in moderate to good yield have been prepared in one-spot reaction by condensation of o-phenylenediamine and different aromatic acid in the presence of ammonium chloride as catalyst at 80-90°C. The reaction is green and economically viable.
Keyword: *o*-Phenylenediamine, economically viable, benzimidazoles.

INTRODUCTION

The development of simple, efficient, environmentally-bengin and economically viable chemical process or methodologies for widely used organic compounds is in great demand [1]. Benzimidazole are present in various bioactive compounds possessing antiviral, antihypertension and anticancer properties[2,3].Compound possessing the benzimidazole moiety express significant activity against several viruses such as HIV[4], Herpes (HSV-1)[5] and influenza[6].

Based on their broad biological functions[7], they are used in clinical medicine[8] as anti-ulcer, anti-tumar and aniti-viral agent[9]. They have Potential use for treatment of diseases such as ischemia-repersion, injury[10a] hypertension[10b] and obesity [10c]. Benzimidazole derivatives have been demonstrated to inhibit Picornaviruses[11,] Polioviruses[12], Enteroviruses[13] etc. Broad antiviral applications of benzimidazole derivatives prompted us to synthesize various N-substituted and 2-substituted benzimidazole and evaluate their antiviral activities against Tobacco mosaic Virus and Sunnhemp rosette virus.

Several synthetic methodologies are available for the synthesis of benzimidazole. Generally, condensation of o-phenylene diamine with carboxylic acid carboxylic acid and their nitrile, imides and orthoesters[14]. Synthesis of 2-substuted benzimidazole from an appropriate o-phenylenediamine and orthoester such as orthoformate, orthoacetate and orthovalerate using$ZrOCl_2.8H_2O$ at room temperature and under microwave irradiation[15]. Simple and efficient method for the convenient synthesis of 2-arylbenzimidazole on reaction with o-phenylenediamine and various aromatic aldehydes using cabalt (II) chloride hexahydrate as a catalyst[16].

The condensation of o-pheneylenediamine with carbonyl compounds in the presence of strong acids such as polyphosphoric acid or mineral acids [17] and other reagents such as I_2/ KI/ K_2CO_3[18], N-halosuccіamide (X= Cl,Br,I)[19], Yb $(OTf)_3$ [20], PEG-100[21], $(NH_4)H_2PW_{12}O_{40}$[22] and palladium as well as microwave irradiation[23] and solid phase reactions[24] are reported in literature.

An alternative synthetic approach using [Fe (III)/Fe(II)] redox mediate[25] oxidation of Schiff base intermediates derivative from o-phenylenediamines and various aromatic heterocyclic aldehyde gave the desire products.

Synthesized differently substituted benzimidazole in very good yield in Solvent free conditions from o-phenylenediamine and aldehydes in presence of BF_3OEt_2 as a catalyst the method is applicable to aromatic, unsaturated and aliphatic aldenydes and to substituted o-phenylenediamines without significant difference[26].

Synthesis of various benzimidazole derivatives under microwave irradiation from simple and substituted ortho phenelendiamine and isonicotinic acid using Si_2 / H_2SO_4 as catalyst.[27].
Trifluroacetic acid (TFA) is introduced as effective catalyst for the selective synthesis of 2-aryl-1-arylmethyle-1H-1, 3-benzimidazole via condensation reaction of o-phenylenediamine derivative and aromatic aldehydes in ethanol/water at room temperature[28].
The use of Bismuth Chloride and rare earth metal triflates such as [$Yb(OTf_3)$] and [$Sc(Otf_3)$] have also been reported[29]. But, synthesis of 2-substituted benzimidazole using Ti(IV) isopropoxide and cumene isppropoxide were recently reported[30].
Several of these reported procedures for the preparation of 2-substitited benzimidazole derivatives were neither versatile nor compatible with differently substituted starting materials.
They are associated with many practical difficulties for example, use of high temperature for the palyphospharic acid mediated condensation reaction led to the formation of by-productrs and benzimidazoles in low yield.

EXPERIMENTAL

The melting points of all synthesized compound were recorded using hot paraffin bath and are uncorrected. ^{1}H NMR spectra ($CDCl_3$) were recorded on Bruker Advance II 400 NMR spectrophotometer using TMS as internal standard. IR spectra were recorded on Perkin-Elmer-1800 FTIR spectrophotometer in the frequency range 4000-450 cm^{-1} in Nujol mull and as KBr pellets. Mass spectra were recorded on a LC-MS Q-Tof Micro, Mass analyzer (Shimadzu). Chemicals used were of AR grade. The purity of the compound was checked on silica gel-G plates by TLC.

General procedure for the synthesis of 2-(4-chlorophenyl)-1H-benzo imidazole (3a)

o-Phenylene diamine (1) (0.01 mole) and p- chlorobenzoic acid (2a) (0.01 mole) both in stoichiometric proportion were taken in ethanol as solvent in presence of NH_4Cl as a catalyst. The reaction mixture was stirred for 2 h at 80 ^{0}c on hot plate. After the completion of reaction, the reaction mixture was cooled and poured in the ice cold water. The granular solid was obtained. It was crystallized from the alcohol, yield 78.88%, m.p. 260 ^{0}C.
IR(KBr) ν = 3190 (-NH), ν = 1591 (C=N), ν =1424 (C=C),ν = 1321 (C-N), ν =852 1,4-disub Aromatic ring and ν =762 1,2-disub Aromatic ring cm^{-1}.
^{1}H NMR ($CDCl_3$) 8.19 ppm (2H, d, Ar-H), δ7.64 ppm (2H, d, Ar-H), δ7.54 ppm (2H, d, Ar-H), δ7.12ppm (2H, d, Ar-H). Mass (m/z) 229 (M^+).

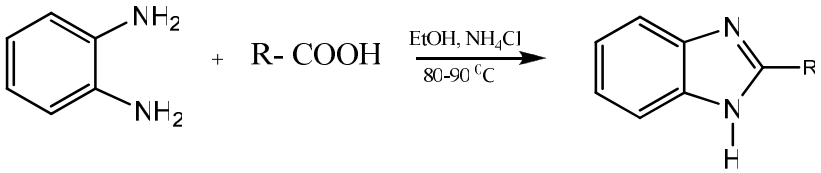
Preparation of 2-(1H-benzo imidazol-2yl)- Phenol (3b)

o- phenylene diamine (1) (0.01 mole) and salicylic acid (2b) (0.01 mole) both in stoichiometric proportion were taken in ethanol as solvent in presence of NH_4Cl as catalyst. The reaction mixture was stirred for 2 h at 80 ^{0}C on hot plate. After completion of reaction, the reaction mixture was cooled and poured in the ice cold water. The granular solid was obtained. It was crystallized from the alcohol, yield 79.18%, m.p.120^{0}C.
IR(KBr) ν = 3429 (-NH), ν = 3360 (-OH), ν = 1576 (C=N), ν =1453 (C=C), ν = 1249 (C-N), ν =749 1,2-disub Aromatic ring cm^{-1}.
^{1}H NMR ($CDCl_3$) 8.00 ppm (2H, d, Ar-H), δ8.05 ppm (2H, d, Ar-H), δ7.25 ppm (2H, d, Ar-H), δ6.84 ppm (2H, d, Ar-H), δ4.22 ppm (1H, s, O-H); Mass (m/z) 210 (M^+).
All other compounds (3c-e) were synthesized in similar manner by treatment of (1) with substituted aromatic acids (2c- e) respectively Table-1.

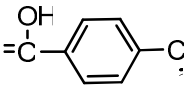
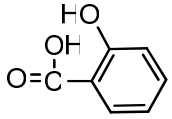
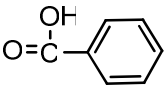
RESULTS AND DISCUSSION

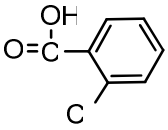
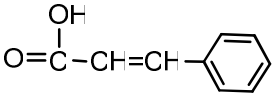
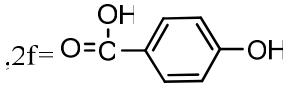
In order to synthesize substituted Benzimidazole derivatives (3), a relatively more versatile yet simplified procedure was perceived. Our argument has been that an instantaneous condensation of o- phenelene diamine and aromatic acid at 80- 90 ^{o}C to affords substituted Benzimidazole with the use of NH_4Cl as catalyst. The strategy worked well affording the desired product in respectable yields. (Table No.1), the

present reaction have been relatively faster, as anticipated, comp aired to those in conventional solution phase synthesis. It is necessary to mention that in all cases the conversion was never 100 %. Some amount of starting material recovered after each reaction.



1 **2** **3**

Where - R = 2a=  ; 2b=  , 2c= 

2d =  , 2e=  ,2f= 

Scheme-1

Table-1: Reaction of o-phenylene diamine (1) (0.01 mole) with different aromatic acids (2) (0.01 mole)

S. No.	Product (3)	-R (2a-e)	Yield (%)	Melting Point ^{0}C	Molecular Formula	Elemental analysis of N Found (Calcd.) (%)		
						C	H	N
1	3a	p-chlorobenzoic acid	78.88	260	$C_{13}H_9ClN_2$	68.15 (68.28)	3.79 (3.97)	12.22 (12.25)
2	3b	Salicylic acid	79.18	120	$C_{13}H_{10}N_2O$	73.80 (74.27)	4.21 (4.79)	13.00 (13.33)
3	3c	Benzoic acid	75.08	90	$C_{13}H_{10}N_2$	80.11 (80.39)	5.01 (5.19)	14.30 (14.42)
4	3d	o-Chloro benzoic acid	90.08	200	$C_{13}H_9ClN_2$	68.15 (68.28)	3.79 (3.97)	12.22 (12.25)
5	3e	Cinnamic acid	72.15	170	$C_{15}H_{12}N_2$	81.60 (81.79)	5.40 (5.49)	12.68 (12.72)
6	3f	p- Hydroxy benzoic acid	78.88	190	$C_{13}H_{10}N_2O$	73.95 (74.27)	4.21 (4.79)	13.00 (13.33)

CONCLUSION

In conclusion we have developed a simple methodology for the preparation of substituted Benzimidazole derivatives (3).The advantage of this method are extremely mild reaction conditions , short reaction time , high yield , simple experimental technique and compliance with green chemistry protocols.

ACKNOWLEGEMENT

Authors are thanks full to Dr.V.G. Thakare , Principal Shri Shivaji Science College, Amravati for providing all necessary facilities to research works and also thanks fully to Director, R.S.I.C.(SAIF), Punjab University, Chandigarh for providing IR, NMR and Mass spectra.

REFERENCES

1. G. A. Meshram and V. D. Pati , *Tetrahedron Lett*.,**50**,1117(2009).
2. D.A. Horton, G.T.Bourne and M.L. Sinythe, *Chem. Rev*.,**103**,893(2003)
3. M. Alamgir, St.C.D Black and N.Top Kumar, *Heterocycl.Chem.,* **9**,87 (2007).
4. (a) A. R. Porcari, R. V. Devivar, L. S. Kucera, J. C. Dreach and L. B. Townsend, *J. Med. Chem.*,**41**,1252(1998); (b) T. Rath., M. L.Morningstar, P.L.Boyer, S.M. Hughes, R.W. Buckheitjr and C.J.Michejda, *J. Med. Chem.*, **41**,4199 (1998).
5. M. T. Migawa, J. L. Girardet, J. A.Walker, G.W. Koszalka, S. D.Chamberjain, J. C. Drach and L. B. Townsend, *J.Med. Chem.* , **41**,1242(1998).
6. I.Tamm, *Science* , **26**,1235(1957).
7. (a.)W.A. Denny, G. W. Rewcastle and B. C.Bauguley, *J. Med. Chem*, **33**,814(1990); (b) L. K. Labanauskas, A. B. Bruksus, P. G. Gaidelis, V. A. Buchinskaite, V. A. Undernaite and V. K. Dauksas, *Pharma Chem. J.*, **34**,353(2000); (c) B.Can-Eke, M. O. Puskullu, E. Buyukbingol and M. Iscan, *Chem. Biol. Intereact*, **113**,65(1998); d) A. Benazzoz, T. Boraud, P. Dub'edat, A. Boireau, J. Stutzmann and C. Gross, *Eur. J. Pharmacol*, **284**,229(1995) (e) R. Sevak, A. Paul, S. Goswami, and D. Santini, *Pharmacol Res*,(2007).
8. P.N. Perston, *Chem. Rev*,**74**,279 (1974); (b) H. Al Muhaimeed, *J. Int. Med. Res*, **25**,175(1927); (c) L. J. Scott, C. J. Dunn and M. Mallarkey Gand Sharp, *Drug,* **62**,1503(2002); (d) P . Venkatesan, *J. Antimicrob Chemother*, **41**,145(1998).
9. (a) P. N. Pesoton, M. F. G. Stevens and G. Tennant, Benzimidazoles and Congeneric Tricyclic Compounds, Part 2 [Jonn Wiley and Sons New York] (1980),(b) R. Cedillo-Rivcer and O. Munoz, *J. Med. Microbial*, **37**,221(1992);(c) B. Chavez, R. Cedillo-Rivera and A. Martiner-Palamo, *J. Portozool*,**39**,510(1992); (d) G. Navarrete-Vazquez, R. Cedillo, A. Hernandez-Compos, L.Yepez, F. Hernandez-Luis, J. Valdez, R. Morales, R. Cortes, M. Hernandez and R. Castillo, *Bioorg. Med. Chem. Lett,* ,**11**, 187(2001).
10. (a) G. D. Zhu, V. B. Gandhi, J .Gong, S. Thomas, Y. Luo, X. Liu, Y. Shi, V. Klinghofer, E. F. Johnson, D. Frost, C. Donawho, K. Jarvis, J. Bouska, K. C. Marsh, S. H. Rosenberg, V. L. Giranda and T. D. Penning, *Bioorg Med. Chem. Lett*, ,**18**,3955(2008); (b) Y. Ogino, N. Ohtake, Y. Nagae, K. Matsuda, M. Moriya, T. Suga, M. Jshikawa, M. Kanesaka, Y. Mitobe, J. Ito, T. Kanno, A. Ishiara, H. Iwaasa, T. Ohe, A. Kanatanitani and T. Fukami, *Bioorg Med. Chem. Lett*, , **18**, 5010(2008); (c) D. I. Shah, M. Sharma, Y. Bansal, G. Bansal and M. Singh, *Eur. J. Med. Chem*, **43**,1808(2008).
11. H. J. Eggers and J.Tomm, *Nature*, **197**,1327(1963).
12. D. G. O'Sullivan, D. Pantic and A. K. Wallis*, Experientia*, **23**,704(1967).
13. N. Novikolova, *Akad Nauk King*, **1**,52(1972).
14. L.M. Dudd, E. Venardou, E. Garcia-Verdugo, P. Licence, A. J. Blake, C. Wilson and M. Poliakoff, *Green Chem*.,**5**,187, (2003).
15. C. S. Reddy and A. Nagraj, *Indian Journal of Chemistry*, **47B**:1154 (2008)
16. A.T. Khan, T. Parvin and et al, *Cheminform*, ,**40,**2339 (2009).
17. (a) P.N. Preston, In the Chemistry of Heterocyclic Compounds: Weissberger, A.Taylor E.C. Eds.: Wiley : New York p. 40,6. (1981); (b) M. R. Grimment, In Comprehensive Heterocylic Chemistry : Katrizky A. R. Ress. C. W. Eds. : Pergamon : Oxfored.,p.457-487(1984). (c) K. Bahrami., M. M. Khodaei and I. Kavianinia, *Synthesis*, 547(2007).
18. P. Gogoi and D. Konwar, *Tetrahedron Lett*.,**47**,79 (2006).
19. H. Fujioka, K. Murai, Y. Ohba, A. Hiramastsu and Y. Kita, *Tetrahedron Lett.,* ,**46**,2197(2005).
20. (a) D.S.Van Vliet, Gillespie and J. J Scicinski, *Tetrahedron lett*,**49**,6237(2008). (b) G. Venket Reddy., V.V. Rama Rao, B. Narsaiah and P. Santhan Rao., *Synth. Commm.*,**32**,2467(2002).
21. C. Mukhopadhyay and P. Kumar Tapaswi, *Terahedron Lett.,* ,**49**,6237(2008).
22. B.Y. Giri, B.L.A. Prbavati Devi, K.N. Gangadhar, L. .K. Vijaya and R.B.N., Prasad *Synthetic Commun*, **3**,2331(2007).
23. M. Curini, F. Epifano, F. Montanari, O. Rosati and S. Taccone, *Synlett*.,**10**,1832(2004).
24. J.P. Robert, Wilson and B. David, *J. Org. Chem.,***58,**7016(1993).

25. C. T. Brain and S. A. Brunton*, Tetrahedron Lett*, **43**,1893(2002).
26. R. R. Nagawade and D. B. Shinde, *Chinese Chemicals letters*, **17(4)**, 453 (2006).
27. B. Guruswamy and R. Arulder, *Pharma Chemica*, ,**3(6)**, 483 (2011)
28. M. R. Mohammadizadesh and S. Z. Taghavi, *E-journal of Chemistry*, **8(1)**, 101 (2011).
29. D.Anastasiou, E. M. Campi, H. Chaouk and W. R. Jackson, *Tetrahedron*, **48**,7467(1992).
30. Z .Wu, P. Rea and G. Wickam, *Tetrahedron Lett*, **41**, 9871(2000).

[RJC-1247/2015]