Research Article

C. Limon Catalyzed Heterocyclisation: Microwave Assisted Rapid One Step Synthesis of Substituted 2-aryl benzoxazoles

Bhagyashri. A. Lole, Pravina B. Piste*
*Organic Chemistry Research Laboratory, Yashavantrao Chavan Institute of Science Satara, (Mah.) India.
***Corresponding author's E-mail:** ppiste321@gmail.com

Received: 21-01-2018; **Revised:** 25-02-2018; **Accepted:** 12-03-2018.

ABSTRACT

The use lemon juice extract as mild and highly efficient acid catalyst offers a convenient, nontoxic, inexpensive reaction medium for the synthesis of 2-aryl benzoxazoles under microwave irradiation condition were described. The procedure is simpler, economical, milder, and faster, including cleaner reactions, high yield of products which makes it a useful and attractive process and is also consistent with the green chemistry theme which affords excellent yields. We have used extract of Citrus limonium species of lemon as natural catalyst for synthesis. As lemon juice provides acidic condition pH 2-3 and percentage of citric acid 5-7% is more, hence it works as natural acid catalyst. The results indicate that lemon juice is the best catalyst for the heterocyclisation process. Adopting green technology, we have successfully applied natural acid catalyst i.e. citrus limon extract for synthesis of 2-aryl benzoxazoles (3a-i) by reaction of 2-amino phenol and substituted carboxylic acid under microwave irradiation. The products were obtained in excellent isolated yields (80-90%). The synthesized benzoxazole derivatives were characterized by IR, 1HNMR, 13CNMR and Mass spectral analysis and evaluated for antimicrobial activity against gram positive (S. aureus) and gram negative (E. coli) bacterial and fungal strain A. niger.

Keywords: Citric acid, Amino phenol, Benzoxazol, Antimicrobial Activity.

INTRODUCTION

The active heterocyclic compounds are one of the main topics of interest for medicinal chemist as it displays various no. of pharmacological activities. Heterocyclic compounds widely occur in nature and in a variety of non-naturally occurring compounds. A large number of heterocyclic compounds are essential to life. Heterocyclic compounds containing nitrogen, oxygen and sulphur belonging to five or six membered heterocycles occupied enormous significances due to their interesting and diverse clinical applications in the field of medicinal chemistry [1]. Oxazoles are five membered heterocycles containing nitrogen and oxygen which are important intermediates in synthesis of several small molecules including amino acid, peptides, heterocyclic precursors for biosensors coupling and photosensitive composition device for proteins and wide range of pharmaceutical properties. Benzoxazol and its derivatives are important scaffold mostly encountered in the drug and pharmaceutically relevant compounds [2-3].They have wide range of biological activities such as antibacterial, antifungal[4], anti-tuberculosis[5], anticancer[6], anti-inflammatory, analgesic[7], antitumor[8], antibiotic[9]. In addition to this benzoxazoles are of enormous importance in material science, especially in fluorescent material [10]. Consequently, the development of synthetic method for preparation of benzoxazoles received considerable attention [11].

Literature reveals that there are generally two types of reactions are used in synthetic methods of benzoxazoles. One method involves transition metal catalysed intramolecular cyclisation of o-haloanilides [12]. Another is the condensation of 2-aminophenol with either carboxylic acid derivatives [13] or aromatic aldehyde [14] under strong oxidative conditions. These methods often suffer from drawbacks, such as the use of strongly acidic conditions, use of toxic catalysts, longer reaction time, lower yield of product, use of solvent and reagents in large excess. To overcome these drawbacks, major efforts have been made for development of environmentally benign new synthetic strategies with lower environment impact. The tremendous progress has been made in synthesis of benzoxazoles by condensation method; still there is scope for development of environmentally benign synthetic approach by using highly efficient catalyst.

We report herein synthesis of substituted benzoxazoles from 2-amino phenol and substituted carboxylic acid by using natural acid catalyst with its antimicrobial evaluation.

MATERIALS AND METHODS

Solvents and reagents were commercially sourced from local suppliers and used without further purification. Melting points were determined in an open capillary and are uncorrected. Products were recrystalized from ethanol as a solvent. The purity of compound checked by the TLC on silica gel G plates. The microwave used for the synthesis of compounds is of ONIDA Company and domestic type. The Infrared spectra were obtained on Perkin Elmer FT-IR spectrometer. The samples were examined as KBr discs 5%w/w.^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avon 300/400 MHz spectrometer using $CDCl_3$/ DMSO as solvent and TMS as internal standard, the chemical shift are reported in ppm.

© Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

General Procedure for Extraction of Citrus Limon

Fresh lemon was purchased from the local market and cut by using knife. Then pieces were pressed manually using domestic presser to extract juice at ambient temperature. Then juice was then filtered through cotton/muslin cloth and then through filter paper to remove solid material and to get clear juice which was used as a catalyst.

General procedure for synthesis of 2-(4-substituted aryl) benzoxazoles

A mixture of 2-amino phenol (0.01mol), carboxylic acid (0.01mol) and 5 ml citric acid in ethanol was taken in beaker and irradiated in micro-oven for 2-3 minutes. The completion of reaction monitored by TLC. The reaction mixture was poured on ice cold water and crude product obtained was filtered and recrystalised from ethanol.

Spectral data of representative compounds

2-Phenylbenzoxazole (Table 2, entry 3a)

IR (KBr): υ_{max}=3057(Ar-H), 2917(-CH), 2845, 1615, 1551, 1445,1342(C-O-C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30-8.27 (2H, m, Ar-H), 7.82-7.79(1H, m, Ar-H), 7.62-7.49 (4H,m, Ar-H), 7.39-7.35 (2H, m, Ar-H).ppm

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 150.7, 141.9, 131.5, 128.9, 127.6, 127.1, 125.1, 124.6, 119.9, 110.6 ppm.

MS (EI): m/z =195 (M+).

2-(4-Chlorophenyl) benzoxazole (Table 2, entry 3c)

IR (KBr): υ_{max}= 3084(Ar-H), 3056, 1616,1594,1552,1482, 1451, 1348(C-O-C), cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17-8.14 (2H, dd, *J* = 7.5, 1.7 Hz, Ar-H), 7.76-7.73 (1H, m, Ar-H), 7.57-7.54 (1H, m, Ar-H), 7.48-7.44 (2H, m, Ar- H),7.37-7.28 (2H, m, Ar-H).ppm

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 150.7, 141.9, 137.7, 129.2, 128.8, 125.6, 125.3, 124.7, 120.0, 110.6 ppm.

MS (EI): m/z = 231(M+).

2-o-Tolylbenzoxazole (Table 2, entry 3f)

IR (KBr): υ_{max}= 3052(Ar-H), 3021, 2914(-CH), 2849, 1620, 1555, 1500, 1470, 1449, 1408, 1344, 1311, 1286, 1241, 1197, 1176, 1139, 1115, 1053, 1016 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18-8.16(m,1H, Ar-H), 7.82-7.79 (m,1H Ar-H), 7.60-7.57 (m, 1H , Ar-H),7.42-7.23 (m,5H,Ar-H), 2.81 (s,3H CH3) ppm;

^{13}C NMR (100 MHz, $CDCl_3$):163.3, 150.3, 142.1, 138.8, 131.7, 130.1, 129.9, 126.2, 126.0, 125.0, 124.3, 120.1, 110.4, 22.2 (CH_3)ppm.

MS (EI): m/z = 209 (M+).

2-p-Tolylbenzoxazole (Table 2, entry 3i)

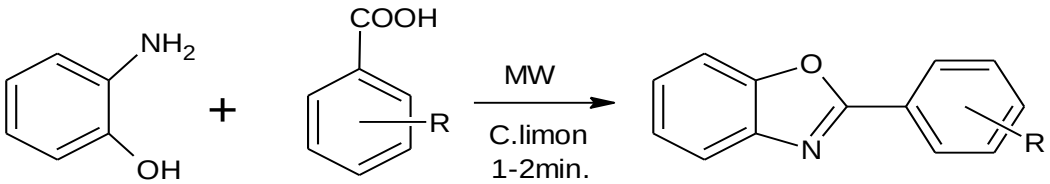
IR (KBr): υ_{max}= 3052,3021(Ar-H), 2914(-CH), 2849, 1620,1555, 1500, 1470, 1449, 1408, 1344(C-O-C), cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18-8.15 (2H, m, Ar-H), 7.79 (1H, m, Ar-H), 7.60-7.57 (1H, m, Ar-H),7.35- 7.28(4H, m, Ar-H), 2.44 (3H, s, CH3)ppm.

^{13}C NMR (100 MHz, $CDCl_3$):163.3, 150.6, 142.1, 142.0, 129.7, 127.6, 124.9, 124.5, 124.3, 119.8, 110.5, 21.2 (CH_3) ppm.

MS (EI): m/z = 210 (M+1).

Scheme



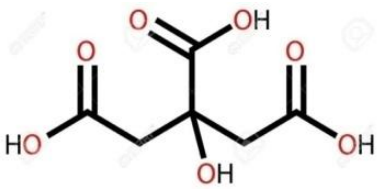
1 2 3a-3i

RESULTS AND DISCUSSION

The synthesis of the 2-(4-substituted aryl) benzoxazole derivatives 3a-3i was obtained by reacting appropriate substituted aromatic carboxylic acids(2) with 2-amino phenol (1) in presence of green reagent i.e. citrus limon extract under microwave irradiation for 1-2 min.. This synthetic route is outlined in the scheme.

Structure of C. Limon:

Major species of citrus family are *Citrus aurantium, Citrus indica, Citrus limonium* which are commonly known as lemon. The lemon, *Citrus limon* (L.) Osbeck, is a species of small evergreen tree in the flowering plant family Rutaceae, native to Asia. In India it is also cultivated in home gardens. For the present work, we used extract of citrus limonium species of lemon. The lemon juice contain85% moisture, 0.5% Vitamin-C, 5-7% citric acid, 1%protein, 11.2% carbohydrates, 1.6 % fibres, 0.9% fat, 0.3 % minerals and also contains organic acids. As lemon juice provides acidic condition pH 2-3 and percentage of citric acid 5-7% is more, hence it Works as natural acid catalyst for heterocyclistion.



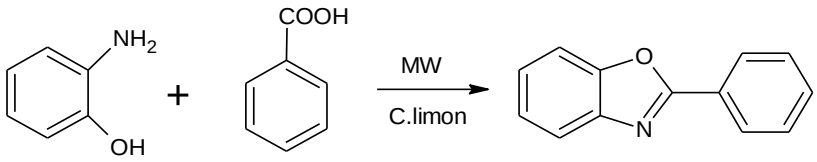
Structure of Citric acid

© Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

In order to validate proposed synthesis, we choose condensation of 2-amino phenol with benzoic acid by use of natural acid catalyst as model reaction for optimization of reaction parameters. Initially, we have studied effect of variety of solvents on reaction system. A series of experiments were conducted using various solvents with both conventional as well as microwave method. It was observed that ethanol was efficient in affording higher conversion (Table 1, entry 9) whereas solvents like THF, DMSO, DMF and methanol provided lower conversions (Table 1, entry 1, 2, 5, 7). The reaction did not proceed in Toluene, 1, 4 dioxane and water (Table1, entry 3, 4, 6). In ethanol, the conversion of 2-amino phenol into benzoxazoles was found to be exclusive. The maximum yield of desired product was obtained by employing the reaction in ethanol by using 5 ml C. limon extract. From the above observations we inferred that, reaction of 2-amino phenol (1.0 mmol.) and benzoic acid (1.0 mmol) with C. limon extract in ethanol as the solvent in microwave for two minute would be the ideal condition for the reaction.

After optimizing the reaction conditions, a series of substituted benzoxazoles were prepared by reacting 2-amino phenol with various carboxylic acids with diverse substituent structural patterns. The results of the reaction are summarized in Table 2. The reactions proceeded smoothly in all cases affording the desired benzoxazoles in good yield. The different functionalities on carboxylic acids such as -Cl, -F, -NO_2 were unaffected by the present reaction conditions. It is noteworthy that several carboxylic acids reacted efficiently forming the products in excellent yield. The structures of the products were determined by IR, ^{1}HNMR, ^{13}CNMR spectroscopy as well as mass spectrometry and the values are in good agreement with literature data.

Table 1: Optimization of reaction conditions[a]

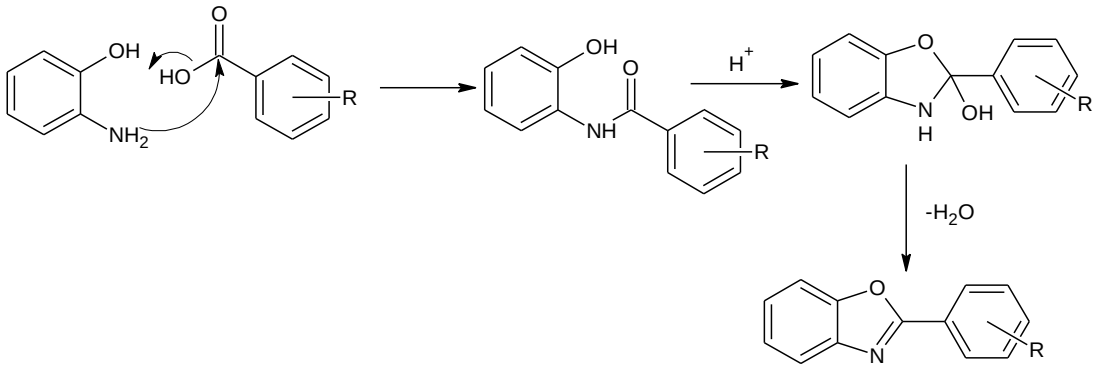


Sr. No.	Solvents (in mL)	Catalyst (in ml)	Reaction time (min.)	% Yield[b]
1	THF	5	60	62
2	DMSO	5	240	57
3	Toluene	5	240	0
4	1,4-Dioxane	5	240	0
5	DMF	5	120	64
6	Water	5	240	0
7	Methanol	5	2	65[c]
8	Ethanol	3	2	69[c]
9	Ethanol	5	2	87[c]

[a]Reaction conditions: 2-amino phenol (1 mmol), benzoic acid (1mmol), catalyst , Solvent (10 ml);

[b] Isolated yields after chromatography; [c]Microwave heating.

The proposed reaction mechanism for synthesis of 2-substituted benzoxazoles from 2-amino phenol and various substituted aromatic acids [15] by using natural acid catalyst is schematically outlined in scheme 2.



Scheme 2: The proposed mechanism for formation of benzoxazole derivatives.

© Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

Table 2: Synthesis of 2-(4-substituted aryl) benzoxazoles by using natural acid catalyst[a] :-

S. No.	Entry	R	Yield[b] (%)	MP[c] (^{0}C)
1	3a	-H	87	[99- 102]
2	3b	-NH_2	85	[11 5-120]
3	3c	-Cl	79	[144-145]
4	3d	-F	81	93[94-96]
5	3e	-2,4 di Chloro	80	[118-119]
6	3f	2-CH_3	86	[68-69]
7	3g	3,5-dinitro	70	[205-207]
8	3h	2-I	77	[150-153]
9	3i	4-CH_3	85	[114-116]

[a]All products were characterized by IR, ^{1}HNMR, ^{13}CNMR, Mass spectroscopy.

[b]Isolated yields after purification, [c]Literature value in parenthesis.

Antimicrobial and Antifungal activity

All the synthesized benzoxazole derivatives 3a-3i were assayed for their in vitro antibacterial activity against S.aureus (gram positive), E.coli (gram negative) and antifungal activity was screened against A. Niger by using cup-plate method. All the antimicrobial analysis results of tested compounds 3a-3i are summarized in Table 3. The compounds 3b, 3c, 3f shows good antibacterial activity against S.aureus. The compounds 3a-3i gives good antibacterial activity against E.coli. The compounds 3b, 3c, 3d, 3e, 3g, 3i show more potent antifungal activity against A. Niger in comparison with standard fluconazole. Remaining compounds shows moderate activity.

Table 3: Antimicrobial analysis of synthesized compounds (3a-3i) -

Compd No.	Antibacterial activity		Antifungal activity
	S.aureus	E.coli	A.niger
3a	16	10	13
3b	**25**	14	**17**
3c	**20**	17	**18**
3d	18	18	**20**
3e	16	22	**20**
3f	**24**	18	12
3g	18	19	**20**
3h	16	20	13
3i	17	17	**15**
Flucanazole	-	-	17
Streptomycin	28	11	-

CONCLUSION

We have used eco-friendly microwave assisted synthetic method for synthesis of substituted benzoxazole derivatives. It is found that C. limon is an efficient catalyst for the synthesis of benzoxazoles. Experimental simplicity, simple and readily available starting material , broad scope of synthesized compounds , green cyclising agent, non toxic nature of catalyst ,short reaction time ,high yield , has capacity for large scale synthesis are the features of current synthesis. Some of the synthesized benzoxazole shows good antifungal and antibacterial activity.

Acknowledgement: Author thanks to Department of chemistry, Y.C. Institute of Science satara for providing research facility and Shivaji University, Kolhapur for providing spectral analysis.

REFERENCES

1. Sadek B, Salem Fahelelbom K. M., Synthesis, characterization and Antimicrobial evaluation of oxadiazole congeners, Molecules, 16, 2011, 4339-4347.
2. McKee M.L., Kerwin S. M., Synthesis, metal ion binding and biological evaluation of new anticancer 2-(2'-hydroxyphenyl benzoxazole analogs of UK 1 Bioorg. Med. Chem., 2008, 16, 1775.

© Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

3. Deorazio R. J., Nikam S. S., Scott I. L. , Sherer B. A., Synthesis of benzoxazoles via intramolecular cyclization of ortho – halobenzanilides using copper fluorapatite catalyst, Chem. Abstr., 137, 2002, 310908.
4. Kaspady M , Narayanswamy V. K., Raju M, Rao G. K., Synthesis, antibacterial activity of 2,4 - disubstituted oxazoles and thiazoles as bioisosteres, Lett. Drug Des. Disc. 6(1), 2009, 21-28.
5. Moraski G. C., Chang M., Structure - activity relationship of new anti-tuberculosis agents derived from oxazoline and oxazole benzyl esters,Eur. J. Med. Chem., 45(5), 2010, 1703-1716.
6. Uckun Fatih M., Forsyth Craig J., Anticancer activity of synthetic analogues of the phorboxazoles, Bioorganic and Med. chem. lett., 11(9), 2001, 1181-1183.
7. Goksen U. S., Kelekci N. G., Goktas O, Koysal Y., Kilic E., Isik S., Aktay G., Ozalp M., 1-Acylthiosemicarbazide, 1,2,4-triazole-5(4H)-thiones, 1,3,4-thiadiazoles and hydrazones containing 5-methyl -2-benzoxazolines : Synthesis, analgesic anti-inflammatory and antimicrobial activities, Bioorganic & Medicinal Chemistry, 15, 2007, 5738–5751.
8. Sierr F. M. P., Pierre A., Burbridge M., Guilbaud N., Novel bicyclic oxazolone derivatives as anti-angiogenicagents, Bioorganic & Medicinal Chemistry Letters, 12, 2002, 1463–1466.
9. Ranabir S. R., Neil L. K., Jill C. M., Christopher T. W., In vivo processing and antibiotic activity of microcin B17 analogs with varying ring content and altered bisheterocyclic sites. Chemistry &Biology, 6(5), 1999, 305-318.
10. Boyer J., Arnoult E., Médebielle M., Guillemont J., Unge J., Jochmans D.,Difluoromethyl benzoxazole pyrimide thioether derivatives: A novel class of potent Non - nucleoside HIV-1 reverse transcriptase inhibitors, J. Med. Chem., 54, 2011, 797.
11. Sheng C, Che X., Wang W., Wang S., Cao Y., Yao J., Miao Z., Zhang W., Design and synthesis of antifungal benzoheterocyclic derivatives by scaffold hopping Eur. J. Med. Chem. 46, 2011, 1706.
12. Evindar G., Batey R. A., Parallel Synthesis of a Library of Benzoxazoles and Benzothiazoles Using Ligand-Accelerated Copper-Catalyzed Cyclizations of ortho-Halobenzanilides, *J. Org. Chem.,* 71, 2006, 1802-1808.
13. Tandon V. K., Kumar M., BF3 Et2O promoted one-pot expeditious and convenient synthesis of 2-substituted benzimidazoles and 3, 1, 5-benzoxadiazepines Tetrahedron Lett., 45, 2004, 4185.
14. Patil S. S., Bobade V. D., Simple and efficient one-pot synthesis of 2-substituted benzoxazole and benzothiazoles, Synth. Commun., 40, 2010, 206.
15. Nahad M. S., Ziarani G. M., Badiei A., Banan A., Sulfonic acid functionalized SBA-15 as a nanoporous acid catalyst was used in the synthesis of 2-Aryl benzoxazoles 4 by the condensation of 2-aminophenol 1 and benzoyl chlorides 2 under microwave irradiation in solvent free reaction conditions, Journal of nanostructure, 3, 2013, 395-401.

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

© Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.