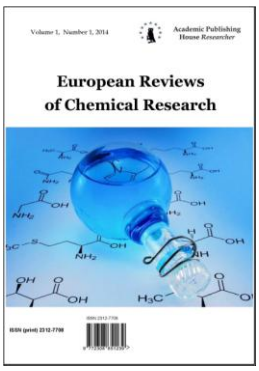
Copyright © 2016 by Academic Publishing House *Researcher*

Published in the Russian Federation
European Reviews of Chemical Research
Has been issued since 2014.
ISSN: 2312-7708
E-ISSN: 2413-7243
Vol. 9, Is. 3, pp. 88-93, 2016

DOI: 10.13187/ercr.2016.9.88
www.ejournal14.com



UDC 547

Boric Acid Catalyzed Synthesis of 2-substituted Benzoxazoles in Aqueous Media

P. Thriveni [a, *], K.P.V. Subba Rao [a], M. Hari Krishna [a], C. Viswanatha [b]

[a] Department of Chemistry, Vikrama Simhapuri University, India
[b] Department of Chemistry, Arba Minch University, Ethiopia

Abstract

We report the synthesis of benzoxazoles using boric acid as catalyst in aqueous media. Synthesis of 2-substituted benzoxazoles derivatives from 2-amino phenol and a variety of aldehydes were developed under mild reaction conditions. The selection and use of water is emphasized as regards methods to minimize environmental impact. On completion of reaction the products were characterized by IR, NMR and Mass Spectra. These methods are more convenient and reactions can be carried out in higher yield.

Keywords: Benzoxazole, Aldehydes, 2-amino phenol, Boric acid, water.

Introduction

Five membered aromatic heterocyclic rings containing a C=N bond, such as benzoxazole is important structural units in natural products and in synthetic pharmaceutical and agrochemical compounds [1-2]. These compounds received a considerable amount of attention for their biological and therapeutic activities [3-4]. Therefore, the development of new methods for the synthesis of nitrogen containing heterocycles is still a focus of intense and containing interest in the organic chemistry as well as in pharmaceutical and agrochemical chemistry. Benzoxazole is an aromatic organic compound with a molecular formula C_7H_5NO, a benzene fused oxazole ring structure and an odour similar to pyridine. Molecules with benzoxazole moieties are attractive targets for synthesis since they often exhibit diverse and important biological activities such as antibiotic [5], antifungal [6], antiviral [7], anticancer [8], antimicrobial [9], and antiparkinson [10] properties. They have also been used as ligands for asymmetric transformations [11].

A variety of oxidants and catalysts have been used for preparation of benzoxazoles. Different catalysts and different methods were also reported for the synthesis of these heterocycles like $Pd(OAc)_2$ [12], $ZrOCl_2 \cdot 8H_2O$ [13], silica sulfuric acid [14], silica supported sodium hydrogen sulfate [15], Indian 190 resin [16], ([Hbim]BF_4) [17], methane sulphonic acid [18], $Cu(OTf)_2$ [19], copper (II) oxide nanoparticles [20], PCC-supported silica gel [21], $In(OTf)_3$ [22], $SnCl_2$ [23], DDQ [24], $BF_3 \cdot OEt_2$ [25], $Mn(OAc)_3$ [26], $PhI(OAc)_2$ [27], $Th^+ClO_4^-$ [28], $BaMnO_4$ [29], NiO_2 [30] and $Pb(OAc)_4$ [31].

* Corresponding author
E-mail addresses: Thrivenivsu@gmail.com (P. Thriveni)

Although these methods worked nicely in many cases, however, some of these suffer from one or more limitations such as low yields, use of volatile or toxic organic solvents, requirement of excess amounts of catalysts or reagents, special apparatus and harsh reaction conditions. Consequently, development of convenient, high yield and environmentally benign procedure for synthesis of benzoxazoles is still a challenging research. Due to the important biological activity of benzoxazoles and in line with our research works in synthesis of this ring system, we wish to report a simple procedure for preparation of 2-aryl benzoxazoles through a condensation reaction of 2-amino phenol and aromatic aldehydes in the presence of boric acid as catalyst in aqueous media.

Experimental section

Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. Solvents were dried using standard methods and distilled before use. The IR spectra were recorded on Perkin-Elmer spectrum RX IFT-IR System using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-400 MHz instruments in $CDCl_3$ with TMS as internal standard. The chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. Chemical shifts are reported in parts per million (δ) relative to $CDCl_3$ (7.27 ppm) for ^{1}H NMR data and $CDCl_3$ (77.0 ppm) for ^{13}C NMR data. Multiplicities are indicated: s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), dd (double doublets), m (multiplet). Column chromatography was performed with silica gel (200-300 meshes). Thin layer chromatography (TLC) was visualized using UV light.

General procedure for the synthesis of benzoxazoles (3a-j)

A mixture of 2-amino phenol (1.0 mmol) and aldehyde (1.2 mmol) in the presence of and boric acid (10 mol %) in water (5 mL) was stirred at room temperature for 30 min. The progress of the reaction was monitored by TLC. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by column chromatography. All the products were identified by spectral (IR, ^{1}H NMR, ^{13}C NMR and mass) and analytical data. The synthetic route was depicted in scheme I.

Spectral data for selected compounds:

2-phenylbenzo[d]oxazole (3a): yield 90%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29-8.27 (m, 2H), 7.82-7.78 (m, 1H), 7.62-7.58 (m, 1H), 7.56-7.53 (m, 3H), 7.39-7.35 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 150.7, 142.0, 131.5, 128.9, 127.6, 127.1, 125.1, 124.6, 120.0, 110.6 ppm.

2-(p-tolyl)benzo[d]oxazole (3b): yield 71%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.4 Hz, 2H), 7.78-7.76 (m, 1H), 7.59-7.57 (m, 1H), 7.36-7.33 (m, 4H), 2.45 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 150.7, 142.1, 129.6, 127.6, 124.9, 124.5, 124.3, 119.8, 110.5, 21.7 ppm.

2-(4-methoxyphenyl)benzo[d]oxazole (3c): yield 96%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.8 Hz, 2H), 7.76-7.73 (m, 1H), 7.57-7.55 (m, 1H), 7.36-7.30 (m, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 3.90 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 162.3, 150.6, 142.2, 129.3, 124.6, 124.4, 119.7, 119.6, 114.3, 110.3, 55.4 ppm.

2-(4-chlorophenyl)benzo[d]oxazole (3d): yield 94%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.4 Hz, 2H), 7.79-7.76 (m, 1H), 7.60-7.58 (m, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.40-7.36 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 150.8, 142.1, 137.8, 129.3, 128.9, 125.7, 125.4, 124.8, 120.2, 110 ppm.

2-(3-chlorophenyl)benzo[d]oxazole (3e): yield 93%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 2.0 Hz, 1H), 8.16-8.13 (m, 1H), 7.81-7.77 (m, 1H), 7.62-7.57 (m, 1H), 7.52-

7.50 (d, *J* = 8.4 Hz, 2H), 7.40-7.36 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 150.7, 141.9, 135.0, 131.5, 130.2, 128.8, 127.6, 125.6, 125.5, 124.8, 120.2, 110.7 ppm.

2-(4-fluorophenyl)benzo[d]oxazole (3f): yield 75%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30-8.25 (m, 2H), 7.80-7.76 (m, 1H), 7.60-7.57 (m, 1H), 7.39-7.35 (m, 2H), 7.25-7.20 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 163.5, 162.1, 150.7, 142.0, 129.9 (d, *J* = 9.0 Hz), 125.1, 124.7, 123.5 (d, *J* = 3.0 Hz), 120.0, 116.2 (d, *J* = 22.0 Hz), 110.6 ppm.

2-(4-bromophenyl)benzo[d]oxazole (3g): yield 84%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 7.2 Hz, 2H), 7.80-7.75 (m, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.60-7.56 (m, 1H), 7.39-7.35 (m, 2H). ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 150.7, 142.0, 132.2, 129.0, 128.9, 126.2, 126.1, 125.4, 125.1, 124.7, 120.1, 120.0, 110.6 ppm.

2-(4-(trifluoromethyl)phenyl)benzo[d]oxazole (3h): yield 82%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.0 Hz, 2H), 7.84-7.79 (m, 3H), 7.64-7.60 (m, 1H), 7.44-7.38 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 150.8, 141.9, 133.1, 132.8, 130.4, 127.8, 126.0, 125.9, 125.9, 125.8, 125.1, 124.9, 122.4, 120.4, 110.8 ppm.

4-(benzo[d]oxazol-2-yl)benzonitrile (3i): yield 79%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 8.8 Hz, 2H), 7.85-7.82 (m, 3H), 7.65-7.62 (m, 1H), 7.46-7.40 (m, 2H).ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 150.9, 141.8, 132.7, 131.1, 127.9, 126.2, 125.1, 120.6, 118.2, 114.7, 110.9 ppm.

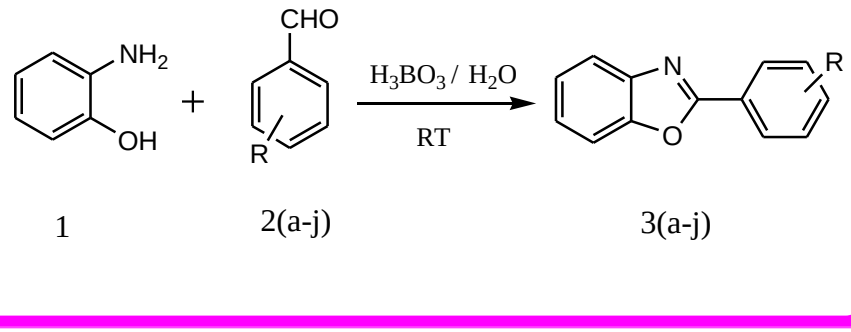
2-(2,4,6-trimethylphenyl)benzo[d]oxazole (3j): yield 67%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 7.85-7.83 (m, 1H), 7.61-7.59 (m, 1H), 7.42-7.39 (m, 2H), 6.99 (m, 2H), 2.37 (m, 3H), 2.30 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 150.6, 141.5, 140.3, 138.4, 128.6, 124.9, 124.2, 120.1, 110.6, 21.3, 20.3 ppm.

Results and discussions

In continuation of our research work using boric acid in organic synthesis here we are pleased to report that amixture of aldehyde, 2-amino phenol in the presence of boric acid (10mol%) in H_2O at room temperature furnished benzoxazoles in good yields (Scheme 1). We chose the reaction between 2-amino phenol and benzaldehyde as the model reaction. First we carried out model reaction in the presence of a catalyst (Table 1, entry 1) and found that the reaction proceed. By using these optimized conditions, various benzoxazole derivatives **3a-j** were synthesized in shorter time as well as in high yields using boric acid as the catalyst. A wide range of aromatic and heteroaryl aldehydes were subjected to prove the general applicability of our present procedure which is summarized in Table 1. It was observed that the aromatic aldehyde bearing an electron donating substituent(–OCH_3)underwent the conversion smoothly as compared to that bearing an electron withdrawing substituent (Table 1). We have synthesized compounds **3a-j** bearing an electron donating substituent(–OCH_3) **3c** with high yields were as compounds **3f, 3g, 3h & 3i** bearing an electron withdrawing substituent (–F, -Br, CF_3, -CN). The reactions are clean and highly selective affording exclusively benzoxazoles in high yields in a short reaction time.

Reactions at different conditions in the presence of boric acid revealed that the best conditions were using water as solvent at room temperature. After completion of the reaction, the catalyst (boric acid) can easily be separated from the reaction mixture by washing the product with water.

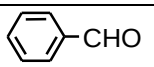
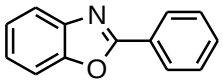
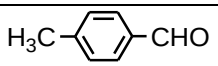
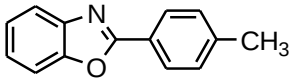
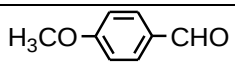
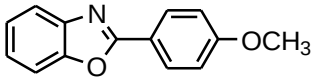
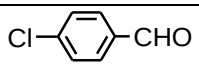
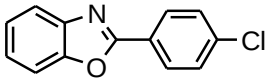
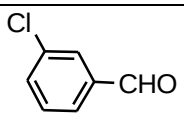
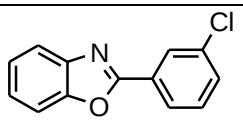
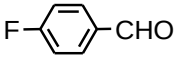
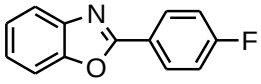
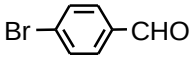
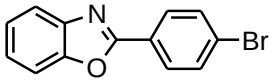
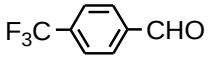
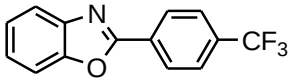
Scheme 1

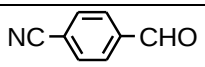
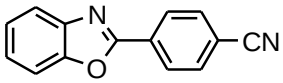
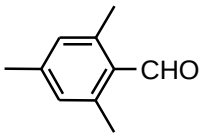
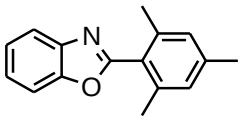


Scheme I: The synthetic route

In our preliminarily investigation on the model reaction of 2-amino phenol and benzaldehyde, it was found that the reaction could be finished under very simple reaction conditions in the presence of boric acid as catalyst in aqueous media which gives the desired benzoxazole product in good yield (Table 1).

Table 1. Synthesis of 2-substituted benzoxazoles from 2-aminophenol and aldehydes

Entry	Aldehyde	Product	Yield (%)
1			90
2			71
3			96
4			94
5			93
6			75
7			84
8			82

9			79
10			67

The main features of our new reaction are as follows:

(1) The simplicity of the system;

(2) The condensation reaction could be performed exclusively using cheap, commercially available chemicals;

(3) Easy separation of products from the reaction mixture;

(4) The method is cost-effective and environmentally benign.

Conclusion

In conclusion, we have demonstrated that 2-substituted benzoxazoles can be synthesized from 2-aminophenols and aldehydes in the presence of boric acid as catalyst in aqueous media in good yields. The present boric acid as catalyst in aqueous media reaction is an alternative route to benzoxazole synthesis using 2-aminophenols and aldehydes.

Acknowledgement

Authors are thankful to our Research Supervisor Dr. P. Thriveni for providing us required facilities and motivation for completion of the research work. We also extend our gratitude towards BRNS, BARC, Mumbai for financial assistance and IICT, Hyderabad for providing us facilities of IR Spectra, ^{1}H NMR for characterization of synthesized compounds.

References

1. McKee, M. L.; Kerwin, S. M. Bioorg. Med. Chem. **2008**, 16, 1775.

2. Mortimer, C. G.; Wells, G.; Crochard, J. P.; Stone, E. L.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. J. Med. Chem. **2006**, 49, 179.

3. Grobler, J. A.; Dornadula, G.; Rice, M. R.; Simcoe, A. L.; Hazuda, D. J.; Miller, M. D. J. Biol. Chem. **2007**, 282, 8005.

4. Rasmussen, K.; Hsu, M. A.; Yang, Y. Neuropsychopharmacology. **2007**, 32, 786.

5. Evans, D.A.; Sacks, C.E.; Kleshick, W.A.; Taber, T.R. *J.Am.Chem.Soc.* **1979**, 101, 6789-6791.

6. Yamato, M. *J. Pharm. Soc. Jpn.* **1992**, 112, 81-99.

7. Song, X.; Vig, B.S.; Lorenzi, P.L.; Darch, J.C.; Townsend, L.B.; Amidon, G.L. *J. Med. Chem.* **2005**, 48, 1274-1277.

8. Kumar, D.; Jacob, M.R.; Reynolds, M.B.; Kerwin, S.M. *Bioorg. Med. Chem.* **2002**, 10, 3997-4004.

9. Yildiz-Oren, I.; Yalcin, I.; Aki-Sener, E.; Ucarturk, N. *Eur. J. Med. Chem.* **2004**, 39, 291-298.

10. Benazzou, A.; Boraund, T.; Dubedat, P.; Boireau, J.M.; Stutzmann, C. *Eur. J. Pharmcol.* **1995**, 284, 299-307.

11. Figge, A.; Altenbach, H.J.; Brauer, D.J.; Tielmann, P. *Tetrahedron Asymmetr.* **2002**, 13, 137-144.

12. Pang, Y.; Hua, W. Tetrahedron Lett. **2009**, 50, 6680–6683.

13. Baltork, I.M, Khosropour, A.R, Catal. Commun. **2007**, 8, 1865–1870.

14. Baltork, I.M, Moghadam, M, Tangestaninejad, *Iran. Chem. Soc.* **2008**, 5, 65–70. 15. Ravi Kumar. K, Satyanarayana, Srinivasareddy. B, *Der Pharma. Chemica*. **2012**, 4, 761–766.

16. Padalkar V.S, Gupta, Phatangare, *Green Chem. Lett. Rev*. **2012**, 5(2), 139–145.

17. Nadaf R.N, Siddiqui S.A, Daniel, *J. Mol. Catal. A Chem*. **2004**, 214, 155–159.

18. Kumar, D.; Rudrawar, S.; Chakraborti, A.K. *Aust. J. Chem*. **2008**, 61, 881–887.

19. Guru, M.M.; Ali, M.A.; Punniyamurthy, T. *Org. Lett*. **2011**, 13, 1194–1197.

20. Saha P, Ramana T, Punniyamurthy T. *J. Org. Chem.* **2009**, 74, 8719–8725.
21. Praveen, C, Kumar K.H, Muralidharan D. *Tetrahedron.* **2008**, 64, 2369–2374.
22. Wang, Bo.; Zhang, Y.; Li, P.; Wang, L. *Chin. J. Chem.* **2010**, 28, 1697–1703.
23. Cho C.S, Kim D.T, Zhang J.Q, *J. Heterocyclic Chem.* **2002**, 39, 421–423.
24. Chang J, Zhao K, Pan S. *Tetrahedron Lett.* **2002**, 43, 951–954.
25. Nagawade R.R, Shinde D.B. *Chin. Chem. Lett.* **2006**, 17, 453–456.
26. Varma R.S, Kumar D. *J. Heterocycl. Chem.* **1998**, 35, 1539–1540.
27. Varma R.S, Saini R.K, Prakash O. *Tetrahedron Lett.* **1997**, 38, 2621–2622.
28. Park K.H, Jun K, Shin S.R, Oh S.W. *Tetrahedron Lett.* **1996**, 37, 8869–8870.
29. Srivastava R.G, Venkataramani P.S. *Synth. Commun.* **1988**, 18, 1537–1544.
30. Nakagawa K, Onoue H, Sugita, *J. Chem. Pharm. Bull.* **1964**, 12, 1135–1138.
31. Stephens F.F, Bower J.D. *J. Chem. Soc.* **1949**, 2971–2972.