ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug343

Synthesis of Biologically Active 2-Arylbenzoxazoles Using "Green Reagent"

Dr. Nagesh Sutar[1]

[1]Associate Professor, Department of Chemistry
Smt. Chandibai Himathmal Mansukhani College (Autonomous), Ulhasnagar, Maharashtra, India

Publication Date: 2025/08/18

Abstract: A chemical reaction has been developed to prepare 2-arylbenzoxazoles which are known for the biological activities. In this protocol, 2-aminophenol was made to react with aromatic aldehydes bearing different substituents, anhydrous bismuth tribromide serving as a catalyst and ethyl alcohol as solvent. The noteworthy attributes of this methodology are the utilization of an eco-friendly catalyst, mild reaction parameters and the achievement of moderate to good yields for the desired products.

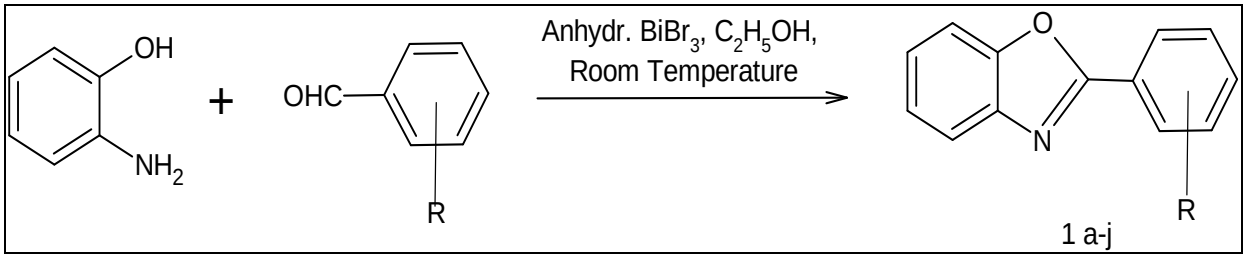
Keywords: *2-Arylbenzoxazole, Biological Activities, Anhydrous Bismuth Tribromide, Eco-Friendly Catalyst, Good Yields.*

How to Cite: Dr. Nagesh Sutar (2025) Synthesis of Biologically Active 2-Arylbenzoxazoles Using "Green Reagent". *International Journal of Innovative Science and Research Technology*, 10(8), 460-464.
https://doi.org/10.38124/ijisrt/25aug343

I. INTRODUCTION

The synthetic as well as naturally occurring organic compounds containing benzoxazole moiety exhibit a wide range of biological activities.[1] Benzoxazoles are structurally related to cyclic nucleotides due to which exhibit tendency to interact with different polymeric entities present into the body of the living organisms.[2] Benzoxazoles possess anti-cancer, anti-HIV, anti-fungal, anti-microbial, anti-bacterial and anti-viral properties.[3] The Benzoxazoles can be prepared by two methods which involve 2 aminophenol to react with carboxylic acids or aldehydes.[4] [5] [6] Even if these methods have own advantages, still some drawbacks like use of polluting organic solvents, structurally intricate and costly catalysts, vigorous reaction conditions and lengthy reaction are noticeable. Looking at the existing strategies, it is necessary to keep on searching green, simple and mild alternate synthetic pathways.[7] Through research work, it has been found that the Bismuth (III) compounds are environmentally friendly reagents and catalytic materials for the various organic conversions. The non-toxicity, stability to air and moisture, easy to handle are some important properties of Bismuth (III) salts.[8] [9] [10] [11] Further, Bismuth (III) salts are found to be mild Lewis acids making them as most suitable catalyst to carry out organic transformations. [12]

The present work demonstrates the effectiveness of anhydrous bismuth tribromide as a catalyst in ethanol at room temperature to prepare 2-arylbenzoxazoles from 2-aminophenol and aromatic aldehydes. (Scheme 1).



Scheme 1

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug343

II. EXPERIMENTAL

Melting points were taken by heating prepared derivatives in open capillary tubes. Thin-layer chromatography (TLC) was used to study the course of reaction. Merck Silica Gel 60F254 was used to prepare TLC plates (0.25 mm thickness). Spots on the plates were irradiated with UV light for the observation. All chemicals and solvents were of Merck or Sigma-Aldrich brands and used as it is.

Procedural details for the synthesis of benzoxazoles (1a–j): To start the procedure, a mixture of 2-aminophenol (0.109 g, 1.0 mmol), aldehyde (1.0 mmol), and ethyl alcohol (3.0 mL) was prepared. Anhydrous $BiBr_3$ (0.031g, 0.1 mmol) was introduced as catalyst. The reaction mixture thus prepared was stirred with Magnetic stirrer at room temperature. Once the TLC confirmed the completion of the reaction, the reaction mixture was filtered and catalyst was separated from the reaction mixture. The product was separated from reaction mixture by extracting it using ethyl acetate. Subsequent evaporation of the solvent resulted in getting the crude product. Purification of the crude product was done via column chromatography. As the product was known compound, its identity was confirmed by comparing its measured melting point with the value reported in the scientific literature.

A reaction between 2-aminophenol and benzaldehyde (R = H) was selected as the model reaction to establish experimental conditions. The reaction of 2-aminophenol with benzaldehyde (R = H) in presence of anhydrous bismuth tribromide as catalyst was selected to find out the optimum reaction parameters. The selection of solvent was the first parameter which was studied. The reaction was performed in different solvents to find out the most effective one in terms of yield of the reaction. Table 1 demonstrate that the reaction is not solvent free in nature (Entry 1). Amng the protic solvents which were tried, ethyl alcohol was found to be most appropriate as it could produce 2-phenylbenzoxazole (1a,Table 3) in highest yield (Table 1, Entry 4). The reaction was not effective with aprotic solvents (Table 1, Entries 5 to 6). Thus, ethyl alcohol was selected as suitable solvent to carry out reaction.

Table 1. Selection of Solvent for the Synthesis of 2-Phenylbenzoxazole (1a) *

Entry	Solvent	Time (min.)	Yield [b] (%)
1	No solvent	More than 180	2
2	$CHCl_3$	80	15
3	CH_2Cl_2	90	20
4	EtOH	30	90
5	CCl_4	150	15
6	MeCN	120	5

*Reaction conditions: 2-aminophenol (1.0 mmol), benzaldehyde (1.0 mmol), $BiBr_3$ (0.1 mmol), solvent (3.0 ml), R.T., [b] Isolated yield

The required catalyst concentration for anhydrous $BiBr_3$ was established by its addition in different amount in the reaction mixture. The compound (1a, Table 3) was obtained with highest yield when 0.1 mmol of catalyst was used. Beyond this point, adding the amount of catalyst did not substantially enhance the reaction yield. Thus, a 0.1 equivalent loading of anhydrous $BiBr_3$ was found to be the most effective for 2-arylbenzoxazole synthesis.

Table 2. Optimization of Catalyst Load for the Synthesis of 2-Phenylbenzoxazole (1a)*

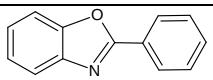
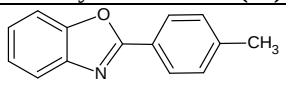
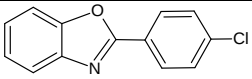
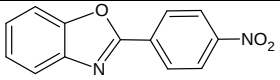
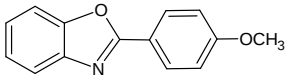
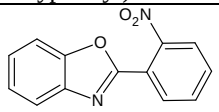
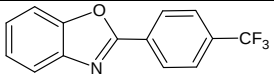
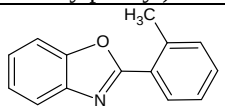
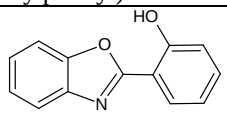
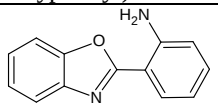
Entry	Amount of $BiBr_3$, mmol	Time (min.)	Yield [b] (%)
1	0.01	75	35
2	0.05	60	45
3	0.10	30	89
4	0.20	30	89

* Reaction conditions: 2-aminophenol (1.0 mmol), benzaldehyde (1.0 mmol), C_2H_5OH (3.0 ml), R.T., [b] Isolated yield

The reaction of 2-aminophenol with a series of structurally diverse aromatic aldehydes was used to check the catalytic proficiency of anhydrous $BiBr_3$ under the established reaction parameters (Scheme 1, Table 3):

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug343

Table 3. Synthesis of 2-Arylbenzoxazoles (1a–j) Using $BiBr_3$ Catalysis*

Entry	R	Product	Time (min.)	Yield [b] (%)	Melting Point (^{0}C)
1	H	 2-Phenylbenzoxazole **(1a)**	30	89	99–101 (101)[13]
2	4-CH_3	 2-(4-Methylphenyl) benzoxazole **(1b)**	40	78	112–113 (113–114)[13]
3	4-Cl	 2-(4-Chlorophenyl) benzoxazole **(1c)**	32	90	149–150 (147)[13]
4	4-NO_2	 2-(4-Nitrophenyl) benzoxazole **(1d)**	45	85	266–267 (266–268)[13]
5	4-OCH_3	 2-(4-Methoxyphenyl) benzoxazole **(1e)**	45	75	102–103 (101)[13]
6	2-NO_2	 2-(2-Nitrophenyl) benzoxazole **(1f)**	50	76	104–106 (104–105)[14]
7	4-CF_3	 2-(4-Trifluoromethylphenyl) benzoxazole **(1g)**	35	89	142–143 (143–145)[15]
8	2-CH_3	 2-(2-Methylphenyl) benzoxazole **(1h)**	42	74	62–65 (63–66)[16]
9	2-OH	 2-(2-Hydroxyphenyl) benzoxazole **(1i)**	30	83	88–89 (87)[18]
10	2-NH_2	 2-(2-Aminophenyl) benzoxazole **(1j)**	32	77	114–116 (115-120˚C)[17]

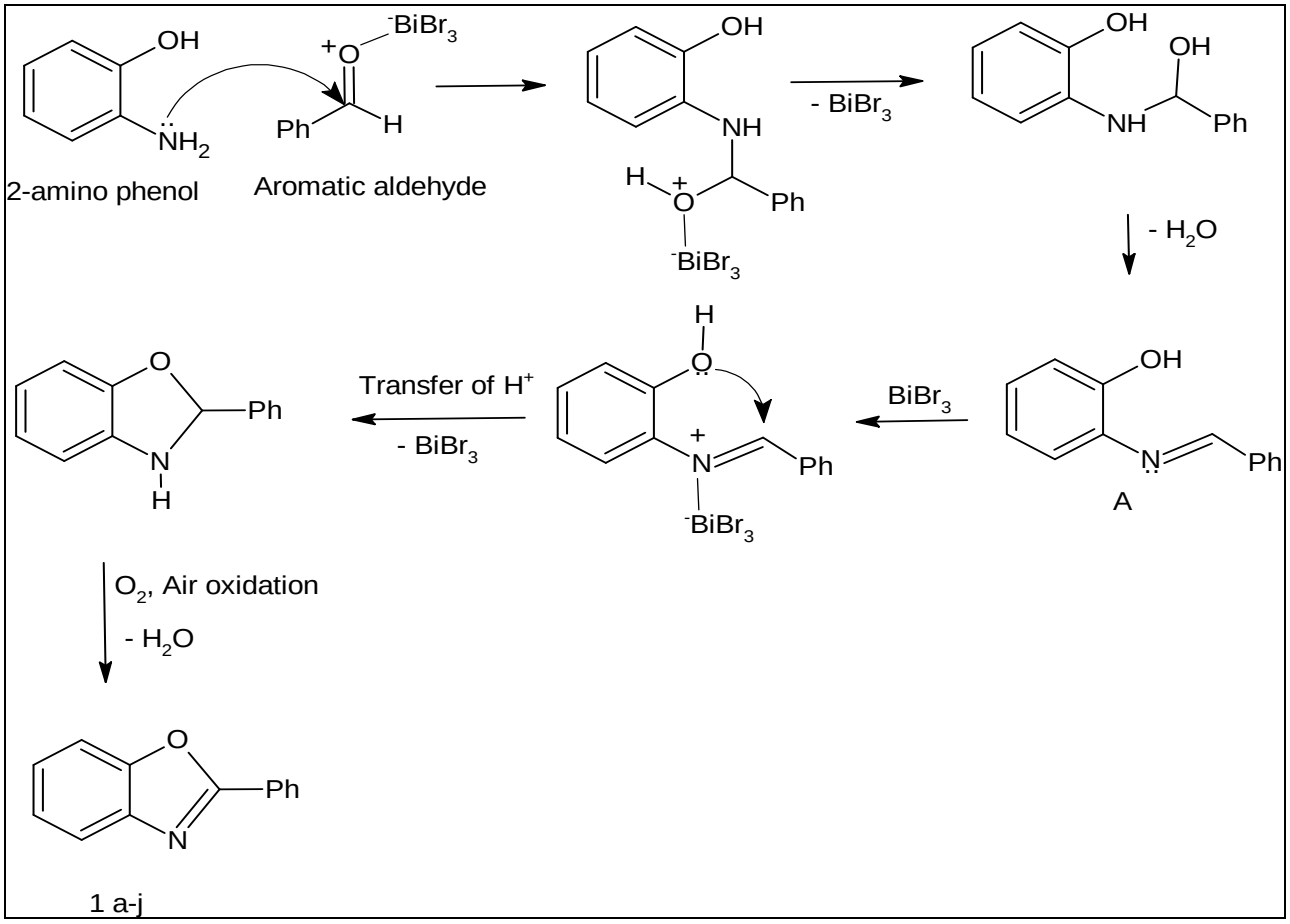
*Reaction conditions: aldehyde (1.0 mmol), 2-aminophenol (1.0 mmol), anhydrous $BiBr_3$ (0.1 mmol) in Ethyl alcohol (3.0 ml) at room temperature, [b] Isolated yield

III. RESULTS AND DISCUSSION

The reaction between 2-aminophenol and various substituted benzaldehydes proceeded successfully under the established parameters because the desired benzoxazoles (1a–j) were obtained in yields ranging from moderate to good, as illustrated in Table 3. A comparative study of the results in Table 3 reveals that the yields were somewhat better for aromatic aldehydes with para-substituted electron-withdrawing groups (Table 3, Entries 3, 4, 7) than for those with electron-donating substituents at para-position (Table 3, Entries 2, 5, 8, 10). The presence of ortho-substituents on aromatic aldehydes leading to steric hindrance near to the reaction center must be a reason for the low yield of the corresponding products (Table 3, entries 8, 9, 10). Benzaldehyde, being sterically unhindered, could undergo a better conversion.

Scheme 2 is an attempt to present the possible mechanism for the synthesis of 2-arylbenzoxazoles as discussed above. $BiBr_3$ being a Lewis acid must be activating the carbonyl group of aromatic aldehydes by coordinating with oxygen atom.[12] Schiff base **A** which is formed during the reaction is also activated by $BiBr_3$ via the coordination with nitrogen atom of imine linkage facilitates its conversion to the desired product.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug343



Scheme 2

IV. CONCLUSION

Anhydrous bismuth tribromide ($BiBr_3$), a Lewis acid, is found to be an efficient catalyst for the preparation of 2-arylbenzoxazoles which involve the reaction of 2-aminophenol with aromatic aldehydes bearing different functional groups. This synthetic pathway was effective to give moderate to good yield of 2-arylbenzoxazoles within a short reaction time. The overall procedure was found to be simple. The easy to handle, environment friendly and non-toxic nature of Anhydrous bismuth tribromide as mentioned in literature further elevates the merit of this pathway.

REFERENCES

[1]. P. Anusha, J. Venkateshwar Rao, "Synthesis and Biological Evaluation of benzoxazole derivatives as new anti-microbial agents, International Journal of Pharmacy and Biological Sciences," Volume 4, Issue 4, Oct-Dec 2014, 83-89.

[2]. L.Turker, E. Sener, I. Yalcin, U. Akbulut, I. Kayalidere, "QSAR of some antifungal- active benzoxazole using the quantum chemical parameters," Scientia Pharmaceutica, 58, 107 113, (1990)

[3]. (i) K.R. Kumar, P.V.V. Satyanarayana, B.S. Reddy, "$NaHSO_4$-SiO_2-Promoted Solvent-Free Synthesis of Benzoxazoles, Benzimidazoles, and Benzothiazole Derivatives," Journal of Chemistry, 2013, 2013, 151273. (ii) S. Sato, Kajiura, M. Noguchi, K. Takehana, T. Kobayashi, T.Tsuji, "AJI9561, a new cytotoxic benzoxazole derivative produced by Streptomyces sp." J Antibiot. 2001, 54: 102–104.

[4]. S. Rezayati, M. Mehmannavaz, E. Salehi, S. Haghi, R. Hajinasiri, S. Afshari Sharif Abad, "Phospho Sulfonic Acid Catalyzed Synthesis of Benzimidazole, Benzoxazole and Quinoxaline Derivatives under Green Solvent at Ambient Temperature," Journal of Sciences, Islamic Republic of Iran, 2016, 27, 51–63.

[5]. S. Wijekoon, C. Gunasekara, L. Palliyaguru, N. Fernando, P. Jayaweera, U. Kumarasinghe, "Solvent-free synthesis and antifungal activity of 3-alkenyl oxindole derivatives" Asian Journal of Green Chemistry, 2022, 6, 297–319.

[6]. A. Datta, "Dowex 50W: A Green Mild Reusable Catalyst for the Synthesis of 2-Aryl Benzoxazole Derivatives in Aqueous Medium," Oriental Journal of Chemistry, 2021, 37, 341–347.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug343

[7]. Fatemeh Hakimi, Mohammad Taghvaee , Elaham Golrasan, Synthesis of Benzoxazole Derivatives Using Fe3O4@SiO2-SO3H Nanoparticles as a Useful and Reusable Heterogeneous Catalyst Without Using a Solvent, Advanced Journal of Chemistry-Section A, 2023, 6(2), 188-197

[8]. Scott W. Krabbe, Ram S. Mohan, Environmentally Friendly Organic Synthesis Using Bismuth (III) Compounds, Top Curr Chem (2012) 311: 45–68.

[9]. G. Sabitha, R. S. Babu, E. V. Reddy, J. S. Yadav, "A Novel, Efficient, and Selective Cleavage of Acetals Using Bismuth (III) Chloride," Chemistry Letters, 2000, 29(9): 1074-1075.

[10]. H. Firouzabadi, I. Mohammadpoor-Baltork, S. Kolagar, "A rapid, selective and efficient method for deprotection of silyl ethers catalyzed by bismuth (III) salts" Synthetic Communication. 2001, 31, 905.

[11]. N. M. Leonard, L. C. Wieland, R. S. Mohan, Tetrahedron 2002, 58, 8373.: N. M. Leonard, L. C. Wieland and R. S. Mohan, "Applications of Bismuth (III) Compounds in Organic Synthesis," Tetrahedron, Vol. 58, No. 42, 2002, pp. 8373-8397.

[12]. Y. Matano and T. Ikegami, in Organobismuth Chemistry, H. Suzuki and Y. Manato, Eds., chapter 2, pp. 21–245, Elsevier, New York, NY, USA, 2001.

[13]. R. S. Varma, R. K. Saini and O. Prakash, "Hypervalent Iodine Oxidation of Phenolic Schiff's Bases: Synthesis of 2-Arylbenzoxazoles," Tetrahedron Letters, Vol. 38, No. 15, 1997, pp. 2621-2622.

[14]. K. Bourgrin, A. Loupy, M. Soufiaoui, "Trois nouvelles voies de synthèse des dérivés 1,3-azoliques sous micro-ondes," Tetrahedron 1998, 54, 8055.

[15]. S. Harsha Vardhan, G. Yashwanthi Sai, B. Ishwarya Lxami and N. Krishnarao, One-pot Synthesis of Benzoxazole analogous catalyzed by Zn $(OAc)_2$, World Journal of Pharmaceutical Research, Volume 14, Issue 8, 984-991.

[16]. K. Ravi Kumar, P. V. V Satyanarayana, B. Srinivasa Reddy, Direct and practical synthesis of 2-Arylbenzoxazoles promoted by Silica supported sodium hydrogen sulphate, Der Pharma Chemica, 2012, 4 (2):761-766.

[17]. Priyanka, Manish Kumar Gautam, Neeraj Kant Sharma, Keshari Kishore Jha, M. Vijayakumar, Design, Synthesis and Pharmacological Screening of 2-(2-(benzo [d] oxazol-2-yl) phenylamino)-n-(substituted phenyl) acetamides as Anti-inflammatory and Analgesic agents, Journal of Advanced Scientific Research, 2014, 5(1): 22-27.

[18]. Heraclio López-Ruiz, Horacio Briseño-Ortega, Susana Rojas-Lima, Rosa Santillan, Norberto Farfán, Phenylboronic acid catalyzed-cyanide promoted, one-pot synthesis of 2-(2-hydroxyphenyl) benzoxazole derivatives, / Tetrahedron Letters 52 (2011) 4308–4312.