SYNTHESIS OF NOVEL DERIVATIVES OF BENZOXAZOLE IN BIS-IONIC LIQUID [BDBDIm]Br

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GRAPHICAL ABSTRACT

Abstract Bis-ionic liquid 3,3-(butane-1,4-diyl)bis(1,2-dimethyl-1H-imidazole-3-ium) bromide ([BDBDIm]Br) was found to be an effective catalyst for the synthesis of novel benzoxazoles using different salicylic acid derivatives and 2-amino-4-chlorophenol at room temperature. The present methodology offers several advantages such as solvent-free conditions, excellent yields, simple procedure, mild conditions, and reduced environmental consequences. The ionic liquid was recovered and reused. All of synthesized compounds were characterized by infrared (IR), NMR, and elemental analyses.

Keywords Benzoxazoles; bis-ionic liquid; room temperature; salicylic acid

INTRODUCTION

The benzoxazole ring is a structural subunit found in a wide class of natural and synthetic compounds showing useful biological properties, such as natural antimycobacterials,[1,2] nonnucleoside reserve transcriptase inhibitors,[3] peroxisome proliferators activated receptor G antagonists,[4] cathepsin S inhibitors,[5] cytotoxic natural products,[6] 5-HT3 receptor antagonists,[7] estrogen receptor B agonists,[8] anticancer agents,[9] and elastase inhibitors.[10] For this reason, benzoxazole derivatives have attracted considerable attention in medicinal research, and a large number of investigations on their synthesis and biological activities have been reported during the past 10 years.[11–16]

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Azo dyes are compounds that contain azo groups linked to methane or aromatic SP²-hybridized C-atom. Azo dyes are well-known class of organic photoactive materials because of their excellent optical switching properties, good chemical stabilities, and high solution process abilities. These materials are widely used in heat transfer printing and textile industries, optical data storage, and photo-refractive polymer industries.

Owing to the important applications of oxazole derivatives, various synthetic methodologies for these compounds have been reported. Generally, the procedures for the synthesis of oxazoles include the Hantzsch reaction, one-pot Friedel–Crafts/Robinson–Gabriel synthesis of oxazoles, the dehydration of oxazolines, condensations of substituted amides with phenacyl bromide in EtOH, the Ugi reaction with ammonia as the amine component, reaction of β-(acyloxy)vinyl azides with triethyl phosphite, and reaction of benzoin carboxylates with formamide. However, these methods suffer from one or more drawbacks that include use of reactive starting materials, long reaction times, poor yields, and harsh reaction conditions.

Ionic liquid allows a new and environmentally safe approach toward modern synthetic chemistry because of the interesting properties of these types of compounds. The unique properties of ionic liquids include negligible vapor pressure, high chemical and thermal stability, good electrical conductivity, and an ability to dissolve a wide range of inorganic and organic compounds.

Ionic liquids offer an attractive alternative to conventional organic liquids for clean synthesis, as they are easy to recycle, lack flammability, and possess effectively no vapor pressure. Compared with classical molecular solvents, ionic liquids are environmentally benign reaction media.

RESULTS AND DISCUSSION

In continuation of our ongoing studies to synthesize heterocyclic and pharmaceutical compounds at mild and practical protocols, herein we report mild and efficient procedures for synthesis of some novel benzoxazoles via the reaction of different salicylic acid derivatives and 2-amino-4-chlorophenol in the presence of bis-ionic liquid [BDBDIm]Br at room temperature (Scheme 1).

To release the efficiency and generality of the reaction, various synthesized azo-bearing salicylic acids were treated with 2-amino-4-chlorophenol in the presence of bis-ionic liquid at room temperature. Compared to the method without ionic liquid, the achieved yields using ionic liquid increased 5–10% and the reaction times with ionic liquid were dramatically shortened to 60–180 min. Therefore, using ionic liquid
exhibited some advantages over the classical condition by improving the reaction yields and reducing the reaction time. Compared to the mono-ionic liquid [BMIM] Br, using bis-ionic liquid [BDBDIm]Br improved yields and the reaction times.

| Entry | Ar                  | Time (min) | Yield (%)<sup>a</sup> |
|-------|---------------------|------------|------------------------|
| 1     | 4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub> | 60 (120)<sup>b</sup> (360)<sup>c</sup> | 90(82)<sup>b</sup> (75)<sup>c</sup> |
| 2     | C<sub>6</sub>H<sub>5</sub>      | 120 (240)<sup>b</sup> (360)<sup>c</sup> | 86 (75)<sup>b</sup> (65)<sup>c</sup> |
| 3     | 2-Cl-4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub> | 90         | 90                     |
| 4     | 4-Cl-2-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub> | 60         | 90                     |
| 5     | 2,4-(NO<sub>2</sub>)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub> | 60 (120)<sup>b</sup> | 95 (80)<sup>b</sup> |
| 6     | 2,4,5-Cl<sub>3</sub>-C<sub>6</sub>H<sub>2</sub> | 90         | 88                     |
| 7     | 2,4-(CH<sub>3</sub>)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub> | 180        | 82                     |
| 8     | 2-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub> | 90         | 95                     |
| 9     | 2,4,6-(CH<sub>3</sub>)<sub>3</sub>-C<sub>6</sub>H<sub>2</sub> | 150        | 85                     |
| 10    | 2-Cl-C<sub>6</sub>H<sub>4</sub> | 120        | 90                     |

<sup>a</sup>All products were characterized by their physical constant, IR, NMR, and elemental analyses.
<sup>b</sup>Yields based upon starting aldehyde in the presence of [BMIM]Br.
<sup>c</sup>In a catalyst-free reaction.
The presence of four ionic centers in ionic liquids [BDBDIm]Br in comparison with two ionic centers in ionic liquid [BMIM]Br helps ionic liquid [BDBDIm]Br to have more ability for the polarization of aldehydes (Scheme 2). The results are summarized in Table 1.

**CONCLUSION**

In conclusion, we have developed a simple, convenient, and efficient protocol for the synthesis of novel benzoxazoles using Bis-ionic liquid as an efficient catalyst. The simplicity, easy workup, and use of inexpensive, environmentally friendly and reusable catalyst are the notable features of this catalytic procedure.

**EXPERIMENTAL**

Chemicals were purchased from Merck and Fluka. All solvents used were dried and distilled according to standard procedures. Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were determined on a Shimadzo FT-IR 8600 spectrophotometer. \(^1\)H and \(^{13}\)C NMR spectra were determined on a Bruker 400 DRX Avance instrument at 500 and 125 MHz. Elemental analyses were done on a Carlo-erba EA1110CNNO-S analyzer and agreed with the calculated values. All solvents used were dried and distilled according to standard procedures.

**Procedure for the Synthesis of the [BDBDIm]Br**

A mixture of 1,2-dimethylimidazole (20 mmol; 1.92 g) and 1,4-dibromobutane (10 mmol; 4.29 g) were irradiated with a laboratory microwave equipped with a thermometer (180 W) for 2 min at 80 °C three times. After cooling to ambient temperature, the residue was extracted thoroughly three times with diethyl ether (10 mL). Impurities were dissolved in the diethyl ether and the reaction mixture was divided into two phases. The ionic liquid was separated from the organic phase using the separator funnel and the remaining solvent in the ionic liquid was evaporated at 80 °C. Finally, the yellow viscous ionic liquid was produced (Fig. 1).

3,3-(Butane-1,4-diyl) bis(1,2-dimethyl-\(1H\)-imidazole-3-iium)bromide: [BDBDIm] Br FT-IR (KBr, \(\nu/cm^{-1}\)): 3075, 2909, 1610, 1520, 1486 (aromatic C=C stretching),

![Figure 1. Structure of ionic liquid [BDBDIm]Br.](image)
1424. $^1$H NMR (DMSO-$d_6$, 500 MHz, ppm): $\delta$ 1.45 (t, 4H), 2.28 (s, 6H), 2.72 (s, 6H), 3.01 (t, 4H), 6.65 (d, $J = 7.5$ Hz, 1H), 6.72 (d, $J = 7.5$ Hz, 1H). $^{13}$C NMR (DMSO-$d_6$, 125 MHz, ppm): $\delta$; 23.2, 41.0, 52.2, 56.1, 127.9, 129.0. Anal. calcd. for C$_{11}$H$_{18}$Br$_2$N$_4$: C, 36.09; H, 4.96; N, 15.30. Found: C, 36.14; H, 5.07; N, 15.24.

**General Procedure for the Preparation of Benzoxazoles 3a–j**

A mixture of salicylic acid derivatives (2 mmol), 2-amino-4-chlorophenol (2.2 mmol; 0.32 g), and [BBDIIm]Br (0.5 mmol; 0.20 g) was stirred at room temperature for the required reaction time according to Table 1. After completion of reaction, as indicated by thin-layer chromatography (TLC), the ionic liquid was separated from the reaction mixture by extraction with $2 \times 15$ mL of water. The solid residue was recrystallized from ethanol to produce novel benzoxazoles 3a–j as pure crystalline products in 82–95% yields (Table 1).

The aqueous phase was concentrated under reduced pressure, washed with diethyl ether, and evaporated under reduced pressure to recover the ionic liquid for subsequent use.

After three successive runs, recycled ionic liquid showed no loss of efficiency with regard to reaction time and yield (Table 2).

To evaluation of basicity of synthesized ionic liquid, titration of 10 mL of aqueous solution of ionic liquid (0.100 M) with 0.100 M of HCl was carried out. The titration curve is given in Fig. 2.

This figure clearly shows that when 15 mL of 0.100 M of HCl is added all of nitrogen atoms of ionic liquid are neutralized. On the other hand, Eq. (1) shows that the neutralization of each basic nitrogen atom of ionic liquid needs 10 mL of acidic solution.

\[
M_{(\text{acid})} \times V_{(\text{acid})} = M_{(\text{base})} \times V_{(\text{base})} \\
0.100 \text{ molar} \times V_{(\text{acid})} = 0.100 \text{ molar} \times 10 \text{ mL} \\
V_{(\text{base})} = 10 \text{ mL}
\]  

(1)

According to the data of the titration curve (Fig. 2), the value of pK$_a$ is 6.2, as regards this reaction was carried out in aqueous media, and then we can use Eq. (2) for calculation of pK$_b$. The pK$_b$ of this ionic liquid is 7.8.

\[
pK_a + pK_b = pK_w = 14
\]  

(2)

We propose a possible mechanism for synthesis of 2-phenyl Benzoxazole derivatives (Scheme 2). In the proposed mechanistic procedure as described in Scheme 2,
initially salicylic acid was activated via depolarization by [BDBDIm]Br to produce 4, followed by nucleophile attack of 2-amino-4-chlorophenol 2, the 5 is prepared and finally, after tautomeration and dehydration, compound 6 was conformed to product 3.

**Analytical Data for Selected Compounds**

**((E))-4-(2-Phenyldiazenyl)-2-(5-chlorobenzo[d]oxazol-2-yl)phenol (3b).**
Cream solid. Mp 253 °C. IR (KBr, cm$^{-1}$): 3362, 1696, 1621. $^1$H NMR (400 MHz, DMSO-d$_6$): 7.16 (dd, $J = 8$ Hz, $J = 1.6$ Hz, 1H), 7.31 (d, $J = 8.4$ Hz, 1H), 7.49–7.52 (m, 4H), 7.62 (s, 1H), 7.6–8.03 (m, 3H), 8.6 (s, 1H), 8.99 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-d$_6$): 106.8, 110.6, 119.3, 121.1, 120.4, 122.3, 124.6, 128.8, 129.2, 130.1, 131.9, 138.8, 146.2, 147.3, 154.5, 158.8, 173.9. Anal. calcd. for C$_{19}$H$_{12}$ClN$_3$O$_2$: C, 65.24; H, 3.46; N, 12.01. Found: C, 65.31; H, 3.52; N, 11.92.

**((E))-4-(2-(2,4-Dinitrophenyl)diazenyl)-2-(5-chlorobenzo[d]oxazol-2-yl)phenol (3e).**
Brown solid. Mp 189–191 °C. IR (KBr, cm$^{-1}$): 3298, 1632, 1605, 1585, 1525, 1348. $^1$H NMR (400 MHz, DMSO-d$_6$): 7.16 (d, $J = 8.8$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.52 (d, $J = 8$ Hz, 1H), 7.62 (s, 1H), 8.02 (d, $J = 7.2$ Hz, 1H), 8.63–8.70 (m, 2H), 8.82 (s, 1H), 8.84–8.85 (m, 1H), 8.98 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-d$_6$): 106.8, 110.7, 119.2, 120.1, 120.4, 123.9, 128.7, 128.8, 129.3, 130.6, 130.9, 138.8, 142.4, 146.2, 148.8, 149.1, 152.6, 158.8, 173.9. Anal. calcd. for C$_{19}$H$_{10}$ClN$_5$O$_6$: C, 51.89; H, 2.29; N, 15.93. Found: C, 51.72; H, 2.32; N, 15.85.

**((E))-4-(2-(2,4,5-Trichlorophenyl)diazenyl)-2-(5-chlorobenzo[d]oxazol-2-yl)phenol (3f).**
Brown solid. Mp 278–280 °C. IR (KBr, cm$^{-1}$): 1411, 1690, 1610, 1572. $^1$H NMR (400 MHz, DMSO-d$_6$): 7.16 (d, $J = 8.8$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.52 (d, $J = 8$ Hz, 1H), 7.62 (d, $J = 8.4$ Hz, 2H), 7.59–7.97 (m, 2H), 8.56 (s, 1H), 8.93 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-d$_6$): 106.9, 110.7, 119.2, 120.1, 120.4, 124.5, 125.7, 128.8, 131.3, 131.7, 132.3, 135.7, 136.0, 138.8, 146.2, 146.7, 156.2, 158.8, 173.9. Anal. calcd. for C$_{19}$H$_9$Cl$_4$N$_3$O$_2$: C, 50.36; H, 2.00; N, 9.27. Found: C, 50.28; H, 1.92; N, 9.19.
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SUPPLEMENTAL MATERIAL

Full experimental details, $^1$H and $^{13}$C NMR spectra, and elemental analyses for this article can be accessed on the publisher’s website.

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