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Synthesis of Bisoxazole and Bromo-substituted Aryloxazoles

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Abstract: Herein, we report a bisoxazole derivative as well as a bromo-substituted oxazole derivatives via a simple approach. The synthesis begins with an inexpensive and readily available starting material, such as 2,5-dimethoxybenzaldehyde, hydroquinone, and *p*-toluenesulfonylmethyl isocyanide (TosMIC). This approach relies on the Van Leusen oxazole method and electrophilic aromatic bromination. The structures of bisoxazole and bromosubstituted aryloxazoles were fully supported by spectroscopic methods (IR, NMR, and HRMS) and further established using single crystal X-ray diffraction studies.

Keywords: heterocycles; 1,3-oxazole motifs; TosMIC; Van Leusen reaction; bisoxazole; electrophilic aromatic bromination

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1. Introduction

The synthesis and structural modification of *N*,*O*-heteroarenes have attracted a large amount of attention from the synthetic community due to their many latent applications, which lead to additional research activity toward expanding new pharmaceuticals. Additionally, these heteroaryl and aryl bromides are valuable intermediates in organic synthesis. Heterocycles are considered as useful scaffolds that induce physicochemical properties, such as lipophilicity, polarity and hydrogen bonding, which lead to the enhanced pharmacological and pharmacokinetic properties of molecules. Among heterocycles, the five-membered heteroaromatic oxazole scaffolds exhibit significant medicinal and pharmacological applications. The presence of heteroatoms in their core structure is involved in hydrogen bonding, *pi–pi* stacking and their interactions with various enzymes and receptors of biological systems. These are relatively stable, active moieties in many pharmaceutical ingredients and extensively observed in nature [1–5]. Additionally, these heterocyclic cores have shown potent activity against drug-susceptible, drug-resistant and multidrug-resistant cancer cell lines [6]. These motifs are capable of binding with various enzymes and receptors, such as histone deacetylase (HDAC), cyclooxygenase-2 (COX-2), and human epidermal growth factor receptor (EGFR) kinase in cancer cells through various non-covalent interactions [7–9]. Furthermore, oxazoles are identified as valuable synthons and have and therapeutic potential for the development of NCEs (new chemical entities) to cure many diseases of clinical importance [10]. Additionally, heterocycles containing oxazole motifs have many applications, particularly for pharmaceuticals [11]. Therefore, the synthesis of heterocycles bearing oxazole moieties is an intriguing aspect in the scientific community.

Oxazole derivatives are found to be an essential constituents in some drugs and further considered as beneficial in modern drug design. Due to their structural and chemical diversity, along with their abundance in natural oxazole motifs, they are considered as a potentially suitable template for the development of anti-cancer research and drug discovery [12,13]. Some representative examples of biologically relevant compounds, such as 1, 2, 5, and 6 bearing an oxazole framework [13–16], are depicted in Figure 1. These compounds [13–16] serve as antibacterial inhibitors of FtSz, COX-inhibitors, antiviral

activity against HCV and CVB, as well as act as potent and selective agonists of free fatty acid receptor 1 (GPR 40).

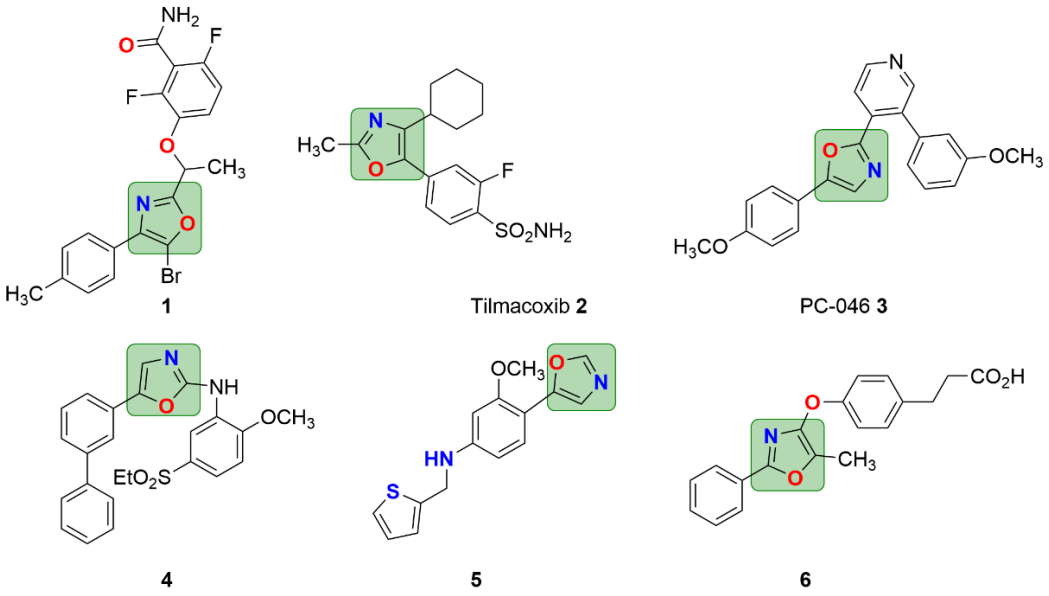


Figure 1. Representative examples of biological relevant compounds (**1**–**6**) bearing an oxazole framework.

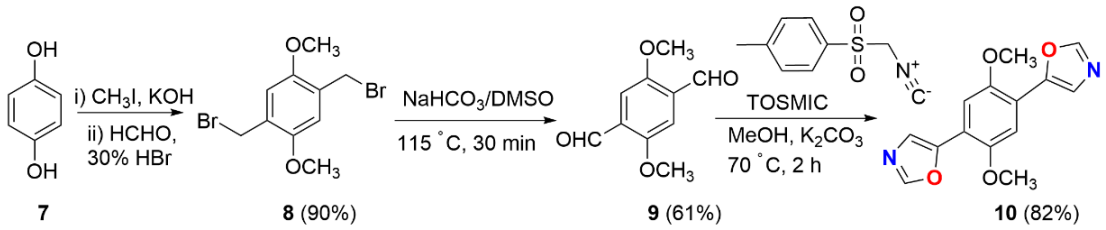
For example, diaryl oxazole-based compound **3** (Figure 1) was reported as a potential agent for the treatment of pancreatic cancer [17]. 2-Anilino-5-aryloxazole derivative 4 was identified as a novel class of potent VEGFR2 kinase inhibitor with good enzymatic and cellular activities [18]. Several compounds containing oxazole moieties have served as clinical drugs or candidates and display a key role in the treatment of various types of diseases, such as antibacterial, antidepressant, antifungal, anti-inflammatory, antimicrobial, antiviral, antitubercular, anticancer, antiparasitic, and antidiabetic roles, and act as adrenergic receptor ligands, T-type calcium channel blockers, prostacyclin receptor antagonists, and transthyretin amyloid fibril inhibitors [19–21]. Therefore, considerable effort has been exerted to construct this privileged heterocyclic motif [22,23].

2. Results and Discussion

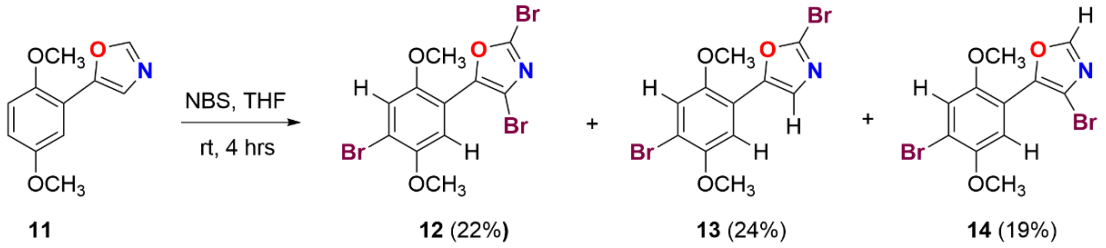
To design various heterocycles, we established new synthetic approaches toward a sequence of heterocycles, such as C_3-symmetric-based heterocycles including carbocyclic cages via the Van Leusen oxazole protocol, through the usage of Toluenesulfonylmethyl isocyanide (TosMIC) as a key reagent [24–28]. TosMIC is a stable, odorless, and colorless solid at room temperature, and it was introduced by the Dutch professor Van Leusen in 1972, named Van Leusen's reagent, and applied in organic synthesis. It is well known as one of the most common building blocks in organic synthesis and is successfully used in the preparation of pyrrole-, imidazole-, and oxazole-based five-membered heterocycles [29,30]. Due to the considerable interest in oxazole motifs as an important structural core in many marketed drugs and its pharmaceutical importance in the new millennium, herein, we conceived a short synthetic sequence to bisoxazole, as well as bromo-oxazoles, under Van Leusen reaction conditions (Schemes 1 and 2).

In view of its importance in diverse fields, we prepared a bisoxazole derivative starting with an inexpensive and readily accessible starting material, such as hydroquinone **7** (Scheme 1). In this context, compound **8** was prepared in excellent yields in two steps (80–90%) through methylation in the presence of CH_3I and KOH followed by bromomethylation with paraformaldehyde in 30% HBr in AcOH. Further, dibromo compound **8** [31,32] was treated with $NaHCO_3$ at 115 °C in DMSO to produce the 2,5-dimethoxyterephthalaldehyde **9** [31] in a 61% yield. Finally, dialdehyde **9** was exposed to

TosMIC in the presence of K_2CO_3 in methanol at reflux (Van Leusen oxazole conditions) to afford bisoxazole **10** in a 78% yield. The bisoxazole compound **10** was fully characterized via spectroscopic parameters (^{1}H NMR, ^{13}C NMR, DEPT-135 NMR, and HRMS data).



Scheme 1. Synthesis of bisoxazole derivative **10**.



Scheme 2. Synthesis of bromo-substituted-oxazole motifs **12**–**14**.

Next, we extended our strategy to prepare a different substituted bromo aryloxazoles. In this context, dimethoxy oxazole compound **11** [26] was subjected to bromination. The electrophilic aromatic bromination of oxazole **11** in the presence of NBS in THF at room temperature for 4 h to deliver the different substituted bromooxazoles **14, 12,** and **13** in 19, 22, and 24% yields, respectively. The structures of bromo-substituted oxazoles **12**–**14** were established based on the spectral data. The tribromo oxazole compound **12** was unambiguously characterized through single-crystal X-ray diffraction analysis (Figure 2). These brominated oxazole scaffolds can be modified further as polyoxazoles useful as a biologically relevant molecules via a well-known cross-coupling protocol. These substituted oxazoles are also of interest in the polymers, agrochemicals, drug discovery research, and aryl bromides are useful intermediates in organic synthesis.

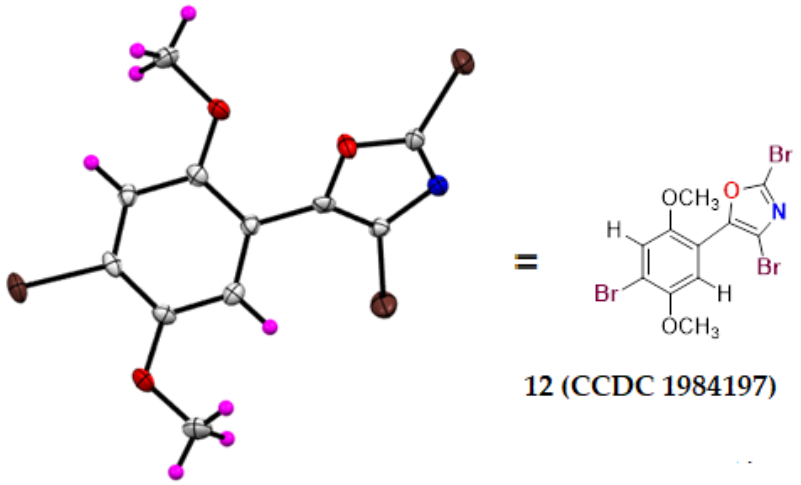


Figure 2. Single-crystal X-ray structure of compound **12**.

The ^{1}H NMR spectrum of bisoxazole **10** revealed the presence of two singlets (two oxazolic protons) at δ 7.91 (1H) indicates the neighboring proton of nitrogen and oxygen

and δ 7.61 (1H) represents the adjacent proton of quaternary carbon and nitrogen for the heteroaryl ring system. In addition, the ^{13}C NMR spectrum of **10** showed three characteristic peaks at δ 149.7, 147.6, and 126.5 of the oxazole ring system, which represents the –CH and quaternary carbon of the oxazole contiguous to N & O atoms (Figure 3). The ^{1}H NMR spectrum of compound **13** displayed three typical aromatic and heteroaromatic chemical shifts at δ 7.16, 7.20, and 7.48 as singlets. Similarly, compound **14** also showed three singlets at δ 7.06, 7.21, and 7.90. We clearly identified the substitution pattern of bromine in the oxazole moiety based on chemical shift values (^{1}H and ^{13}C), such as δ 7.48, 129.0, 7.90, and 150.5, which are adjacent to N, O and N, and the quaternary center of both aryl and heteroaryl systems, respectively. Further, we support the substitution pattern with the DEPT/HMBC method (Figure 3). The NMR spectra of these all are provided in the Supplementary Material.

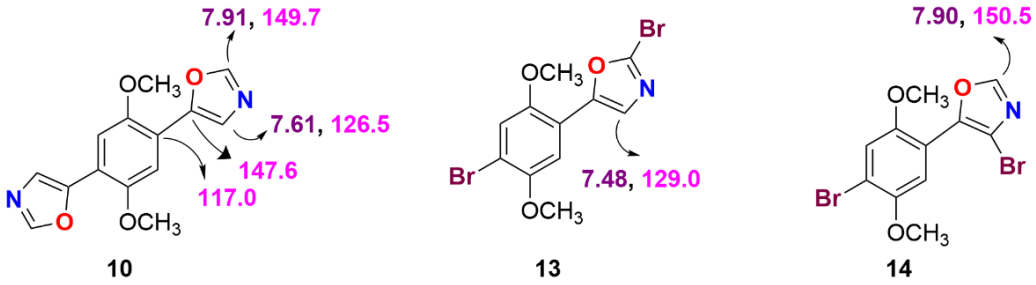


Figure 3. Correlation of ^{1}H and ^{13}C NMR value (s) of different oxazole frameworks.

3. Materials and Methods

3.1. General Information

2,5-Dimethoxybenzaldehyde, TosMIC, hydroquinone, NBS, and other essential reagents, chemicals, and necessary solvents were used as received and directly obtained from commercial suppliers without any further purifications. Thin-layer chromatography (TLC) plates were made on 10 × 5 cm glass plates layered with commercial-grade Acme's silica gel (GF-254) containing 13% $CaSO_4$, which acts as a binder. Reaction progress was analyzed using a chromatographic technique (TLC analysis) with suitable solvent systems (EtOAc/Pet ether), and observation was performed using UV, iodine spray and immersion in $KMnO_4$ solution. Column purification was performed using 100–200 mesh silica gel in all cases with suitable solvent systems. The boiling range of petroleum ether used in column purification was around 60–80 °C. All IR samples were recorded using DCM and chloroform as solvents on a Nicolet Impact-400 FTIR spectrometer. Nuclear magnetic resonance (NMR) spectra (^{1}H, ^{13}C and DEPT 135) were recorded on 400 and 500 MHz spectrometers (Bruker) with $CDCl_3$ solvent, and chemical shifts (δ ppm) were reported relative to internal standards, such as TMS. The *J* values (coupling constants) are given in Hz. Mass spectra (HRMS) were recorded under positive ion electrospray ionization (ESI, Q-TOF) mode. Compounds **8** [32], **9** [31], and **11** [26] were prepared according to the literature, and the data were consistent with the reported values.

3.2. Synthesis and Characterization

3.2.1. 5,5′-(2,5-Dimethoxy-1,4-phenylene)Bis(oxazole) (**10**)

TosMIC (220 mg, 1.13 mmol, 1.1 equiv. for each formyl group) and K_2CO_3 (568 mg, 4.11 mmol, 4 equiv for each formyl group) in MeOH (10 mL) were added to a stirred solution 2,5-dimethoxyterephthalaldehyde (**9**) [31] (100 mg, 0.51 mmol, 1.0 equiv.). Later, the resulting reaction mixture was heated to 70 °C for 2 h. At the end of the reaction, which was monitored using TLC, methanol was removed under vacuum conditions, and an additional crude reaction mixture was purified via column chromatography with a 100–200 mesh silica gel column. Elution of the silica gel column with 40% ethyl acetate in petroleum ether gave the desired dimethoxy oxazole **10** in pure form as colorless needles;

TLC R_f = 0.57 (petroleum ether/ethyl acetate = 50:50); yield: 115 mg (82%); Mp: 239–241 °C; IR (neat, cm^{-1}): υ_{max} = 3115, 2932, 2847, 1696, 1503, 1456, 1376, 1330, 1403, 1229, 1210, 1114, 1051, 1032, 944, 851, 638; ^{1}H NMR (500 MHz, $CDCl_3$):δ (ppm) = 7.91 (s, 2H), 7.61 (s, 2H), 7.35 (s, 2H), 3.98 (s, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 150.0, 149.7, 147.6, 126.5, 117.0, 108.6, 56.1; HRMS (ESI, Q-ToF): *m*/*z* calcd. for $C_{14}H_{13}N_2O_4$ $[M + H]^+$ 273.0870, found: 273.0864.

3.2.2. Synthesis of Bromo-Oxazoles **12**–**14**

NBS (690 mg, 3.80 mmol) was added to a stirred solution of dimethoxy oxazole **11** [26] (500 mg, 2.43 mmol) in THF (20 mL). Afterward, the resulting mixture was stirred at room temperature for 4 h. The solvent was evaporated under reduced pressure, and the crude product was purified via silica gel column chromatography using 0–1% ethyl acetate in petroleum ether as an eluent to deliver the bromo-substituted aryloxazoles 12, 13, and 14 in 22%, 24%, and 19% yields, respectively.

3.2.3. 2,4-Dibromo-5-(4-Bromo-2,5-Dimethoxyphenyl)oxazole (**12**)

Colorless needles; TLC R_f = 0.92 (petroleum ether); yield: 237 mg (22%); Mp: 164–166 °C; IR (neat, cm^{-1}): υ_{max} = 3250, 2905, 2827, 2803, 1690, 1498, 1488, 1388, 1285, 1242, 1215, 1195, 1070, 1041, 1025, 997, 856, 771, 568; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.20 (s, 1H), 7.00 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 151.5, 150.1, 149.3, 133.1, 117.5, 115.6, 115.0, 114.2, 113.7, 57.1, 56.5; HRMS (ESI, Q-ToF): *m/z* calcd. for $C_{11}H_{10}Br_2NO_3$ $[M + H]^+$ 361.9004, found: 361.9022.

3.2.4. 2-Bromo-5-(4-Bromo-2,5-Dimethoxyphenyl)oxazole (**13**)

Colorless needles; TLC R_f = 0.85 (petroleum ether); yield: 215 mg (24%); Mp: 137–139 °C; IR (neat, cm^{-1}): υ_{max} = 2911, 2664, 2413, 2315, 1501, 1491, 1369, 1290, 1247, 1217, 1186, 1161, 1117, 1061, 1032, 961, 949, 868, 768; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.48 (s, 1H), 7.20 (s, 1H), 7.16 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 151.5, 150.5, 149.9, 132.2, 129.0, 116.7, 115.8, 112.4, 109.1, 57.1, 56.3; HRMS (ESI, Q-ToF): *m*/*z* calcd. for $C_{11}H_{10}Br_2NO_3$ $[M + H]^+$ 361.9022, found: 361.9021.

3.2.5. 4-Bromo-5-(4-Bromo-2,5-Dimethoxyphenyl)oxazole (**14**)

Colorless needles; TLC R_f = 0.76 (petroleum ether); yield: 175 mg (19%); Mp: 123–125 °C; IR (neat, cm^{-1}): υ_{max} = 3132, 2969, 2840, 2325, 1490, 1386, 1369, 1315, 1290, 1217, 1180, 1161, 1115, 1061, 1029, 986, 861, 766; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.90 (s, 1H), 7.21 (s, 1H), 7.06 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 151.6, 150.6, 150.1, 145.2, 117.5, 115.1, 114.4, 114.2, 114.0, 57.1, 56.6; HRMS (ESI, Q-ToF): *m/z* calcd. for $C_{11}H_{10}Br_2NO_3$ $[M + H]^+$ 361.9022, found: 361.9027.

3.3. Data Collection and Refinement Details

The X-ray structure of compound **12** was determined using single-crystal X-ray diffraction. Single crystals of compound **12** were obtained from ethyl acetate in hexane solvent at room temperature. Crystal data were collected with graphite monochromatized $M_0K\alpha$ radiation (λ = 0.71073) on a Rigaku Saturn 724+ diffractometer using ω scans at a temperature of 293 K. The structures were solved via direct methods using Olex-2 [33] and ShelXL-97 [34] and refined using full-matrix least-square minimization based on F^2. ORTEPs were drawn using the Mercury program [35]. X-Ray crystallographic data and refinement parameters for compound **12** were tabulated in an SI file and deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC No: CCDC-1984197. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif (accessed on 15 February 2020). Selected X-ray data of 12: $C_{11}H_8Br_3NO_3$, M = 441.91, orthorhombic space group = $Pca2_1$, unit cell: a = 20.626 (8) $Å^3$, b = 9.0594 (5) $Å^3$, c = 7.1357 (3) $Å^3$, α = 90°, β = 90 °, γ = 90°, Z = 4, ρcald = 2.201 mg/m^3, F(000) = 840, λ = 0.71073 Å,

$\mu = 9.074\ mm^{-1}$, total/unique reflections = 6776/2346, final *R* indices [*I* > 2sigma (*I*)]: R1 = 0.0293, ωR2 = 0.0572, *R* indices (all data): R1 = 0.0345, ωR2 = 0.0598.

4. Conclusions

In summary, we successfully synthesized a bisoxazole derivative and various bromo-substituted aryloxazoles in good yields. These compounds were synthesized through the combination of Van Leusen reaction and bromination with NBS used as key steps. Finally, the structures of these oxazoles were confirmed using NMR, HRMS, and X-ray diffraction. It is worth noting that the oxazole frameworks may become valuable candidates for applications in medicinal/pharmaceutical and drug delivery.

Supplementary Materials: The following are available online, ^{1}H, ^{13}C, and DEPT NMR spectra of compounds **8**, **9**, **10**, **11**, **12**, **13**, and **14**. Check CIF report and cif file for the title compound **12**.

Author Contributions: Investigation, data curation, and writing—original draft preparation, S.R.C.; resources and writing—review and editing, S.R.C. and S.K.; conceptualization, data curation, and writing—original draft preparation, S.R.C. and S.K. All authors have read and agreed to the published version of the manuscript.

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