Chapter 6

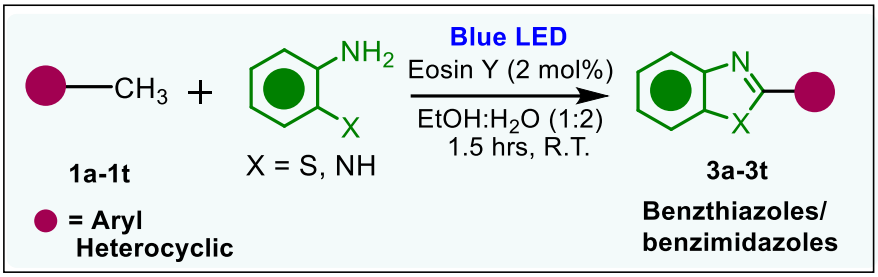
Summary and Conclusions

Heterocyclic compounds are cyclic structures in which one or more ring atoms are non-carbon atoms, such as sulfur (S) and nitrogen (N). Sulfur and nitrogen-containing heterocyclic compounds hold significant biological relevance due to their unique structural and chemical properties, contributing to their involvement in various biological processes and their potential as therapeutic agents. These compounds play essential roles in drug discovery, medicinal chemistry, and the development of bioactive molecules. Many nitrogen sulfur-containing heterocyclic compounds have applications in pharmaceutical research, agriculture science, and drug discovery. Given the above facts, the thesis entitled, 'Green Approaches for the Synthesis of Some Biologically Relevant N, and S Containing Organic Compounds,' embodies the synthesis of biologically important compounds containing nitrogen and sulfur atoms and their structural assignments. The contents of the thesis have been divided into five chapters. The investigations and findings are described in four chapters (**Chapters 2 to 5**). Each chapter is independently complete and consists of an introduction, results, discussion, experiment, and references.

Chapter 1 provides a general introduction and literature review of the synthesis and applications of some main nitrogen and sulfur-containing organic compounds classes.

Chapter 2 describes a novel and efficient approach for synthesizing benzothiazoles and benzimidazoles under visible light irradiation using Eosin Y as a photocatalyst, ethanol: water as a green solvent, and atmospheric air as an oxidant. This method combines C–H

bond cleavage, dioxygen activation, and oxidative C–S, C–N bond functionalization. Using an organic dye, Eosin Y, provided a mild and economical catalytic system to synthesize a series of benzothiazoles and benzimidazoles in good to excellent yields. (**Scheme A**).



Scheme A

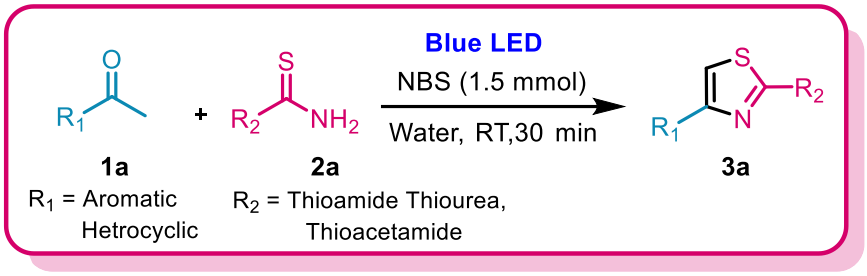
To determine the optimal conditions, we started our observations using a visible-light photoredox reaction of methylarene **1a** with 2-aminothiophenol **2a**, which was selected as the model reaction to optimize the reaction conditions under blue LED irradiation in ambient air at room temperature. Firstly, we investigated the role of various photocatalysts using ethanol as a solvent. Eosin Y was the most active catalyst, yielding product 3a in 52%. Next, different solvents were optimized, and water gave a good yield of 60%. It was observed that using water/ethanol in a 1:1 ratio led to a marginal increase of 70% in yield. Encouraged by the finding, a different ratio of ethanol and water was tried. We got the best result (90%) using a mixture in the ratio of 1:2. Further, we tried the reaction without blue LED but failed to give the desired product. Then, we varied the loading of Eosin Y from 3 mol% to 4 mol% and found the exact yield on increasing the mol% of the photocatalyst.

We tried extending the reaction time but failed to get a better yield of product **3a**. After that, under the same reaction condition, the influence of light on the reaction was investigated, and no product was formed in the absence of light, indicating the essential role of light irradiation. To further explore the impact of different light sources, purple, green, and white LED lights and a 20W CFL were used instead of the blue LED. The results showed that these light sources produced comparable yields of 65-69%. In addition, the effect of atmospheric air was examined, and the reaction under oxygen produced almost the exact yield as under air.

After determining the optimal reaction system, we further explored the range of photocatalytic condensation reactions of aromatic methyl arenes with different substituents. When the methyl arene has -F, -Cl, -Br, and -CH_3 in the p-position, it is found that the yield with electron-withdrawing groups is superior to that with electron-donating groups. The target products can be obtained in good yields when the substituent is in the m- and oppositions. We also tried to use heteroaromatics to react with methyl arene, and we found that the heteroaromatics gave good yields of 83% to 84%. All the reactions were carried out at room temperature in the presence of oxygen as an oxidant. This methodology showed a broad substrate scope, while the desired products were obtained in good to excellent yields.

Chapter 3 explores a highly efficient and greener approach for C–S bond formation in synthesizing 2,4-disubstituted thiazoles through cascade functionalization of acetophenone.

This novel method utilizes methyl aryl ketones, N-bromo-succinimide (NBS), and thioamides in water as a green reaction medium under visible light irradiation. Using NBS as a bromine source, the reaction occurs through an in situ α-bromination method (**Scheme B**).



Scheme B

To optimize the reaction conditions for synthesizing 2,4-disubstituted thiazoles **3** from acetophenone **1a**, NBS as a brominating reagent, and thiobenzamide **2a**, was selected as a model reaction. To optimize the reaction conditions, we performed the reaction under visible light (a 15 W blue LED of 450 nm) irradiation at room temperature, using Eosin Y (2 mol%) as a photocatalyst and water as a solvent, and we got 75% yield of the desired product **3a** in 60 min. This result encouraged us to test various polar and non-polar solvents, such as ethanol, DCM, acetonitrile, THF, toluene, and dimethyl carbonate (DMC), to study their effect on reaction efficiency; however, only 35–66% yields of products were obtained.

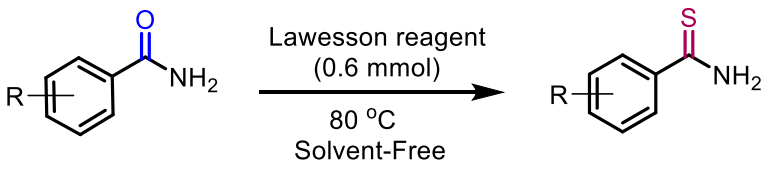
Furthermore, we tested various photoredox catalysts such as rose bengal, acridine red, and rhodamine B in water but did not effectively provide the target product. Then, we tried the

reaction under catalyst-free conditions in water, and surprisingly, 90% yield of the product was obtained in only 30 minutes. This may be due to the photocatalysts' separation process or the product's instability in the presence of photocatalysts. The reaction was also carried out using the conventional method, refluxing in water without blue light, which gave only 70% yield of the product. After that, the reaction was carried out in the dark, but we did not get any yield of the product, showing the significance of light irradiation in this reaction. Subsequently, various light sources were also investigated, but the yield was unsatisfactory. Without a solvent, the reactants were not converted into the product. So, the optimized conditions for the synthesis of the 2,4-disubstituted thiazole 3a are acetophenone **1a** (1.0 mmol), NBS (1.5 mmol), and thiobenzamide **2a** (1.2 mmol), with water as a solvent under 15 W blue LED irradiation.

With the optimized reaction conditions in hand, we focused on studying the scope of this reaction with various methyl aryl ketones and thioamides. Both electron-withdrawing (F, Cl, Br, NO2, and CN) and electron-donating (OMe and Me) groups on the phenyl ring of methyl aryl ketones gave moderate to good yields. Substituted thioamides, such as methyl and halogen thioamides, reacted with methyl aryl ketones and gave the corresponding products in good yields, and heterocyclic thioamides gave the products in moderate yields. Encouraged by these results, we studied the synthesis of 2,4-disubstituted thiazoles from thiourea/alkyl thioamides with methyl aryl ketones under similar reaction conditions. A series of substituted acetophenones were examined to evaluate the electronic influence of substituents on the aromatic ring of acetophenone. The results showed that electron-

withdrawing groups (F, Br, and NO2) and electron-donating groups (Me and OMe) provided good to excellent yields of 80% to 85% of the corresponding. To further expand the scope of this methodology, the reaction of different methyl aryl ketones with thiourea and thioacetamide was also investigated, and the desired products were obtained in good yields of 83–85%. Hence, there is no electronic influence of substituents on the benzene ring on the product yields. Due to the wide range of functional group tolerability, this is a universal method for forming thiazole under catalyst-free and base-free conditions at room temperature. The advantages of this procedure are that it is photocatalyst- and metal-free, has mild reaction conditions, is operationally simple, and affords high yields of the products.

Chapter 4 presents a simple, straightforward, and highly efficient method for synthesizing thioamide derivatives from amides/nitriles and Lawesson reagents in solvent-free conditions at 80 ^{O}C. The cheap and readily available LR acted as the sulfur source to assemble the thioamide derivatives. This reaction represents effective access to thioamides from readily available starting materials with good functional group tolerance. The prominent advantages of this method are shorter reaction time, chromatography-free, and easy work-up. (**Scheme C**).



Scheme C

At the beginning of our study, the reaction between amide/nitrile **1a** (1.0 mmol) and Lawesson reagent (0.6 mmol) was carried out as the model substrate for synthesizing the desired product **2a**. This included different parameters like solvent, temperature, and molar ratio of the reactant. First, the model reaction was carried out in different non-polar and polar solvents. In non-polar solvents toluene, benzene at its boiling temperature of 1h gave the product 2a in 45, 50% yield respectably, and in the case of polar aprotic solvents like tetrahydrofuran, dichloromethane, acetonitrile, at its refluxed temperature gave the product **2a** but no satisfactory yield was obtained. Then, we examined polar protic solvents like methanol, ethanol, and water, which failed to give the desired product **2a**.

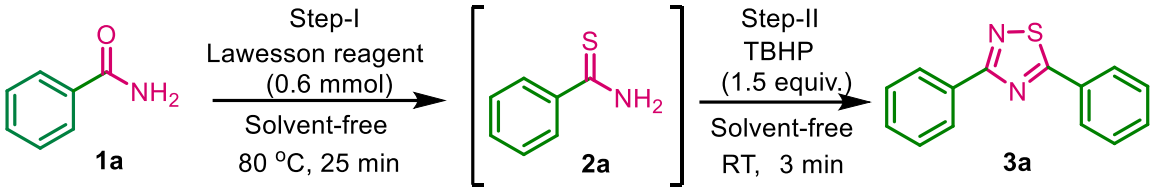
In order to improve the yield of the product in a greener manner, we have switched to a solvent-free process. From the environmental perspective, green chemistry has greatly appreciated in recent years. According to one of the principles of green chemistry, toxic solvents in organic synthesis should be replaced with greener alternatives (e.g., water, Ionic liquids, supercritical CO2, bio-based green solvents, etc.), or the chemical reaction should be favored under solvent-free conditions. The development of solvent-free protocols appears to be an ideal case because solvent-free reactions reduce environmental pollution and are also high-yielding and cost-effective. To our enchantment, the yield improved significantly, giving an 85% yield in 25 min at 80 ^{O}C when the reaction was performed without solvent. Solvent-free conditions increase the rate of reaction due to an increase in collision frequency, which decreases the reaction time; this could be the reason that resulted

in a high yield in solvent-free conditions. Next, other factors, such as temperature and amount of the Lawesson reagent, were also evaluated. Increasing the reaction temperature above 80 ^{O}C didn't significantly affect the yield of **2a**. Meanwhile, when temperature decreases, our desired product 2a yields also decrease. It is important to mention that the reaction temperature affects the yield of the product and increases the amount of Lawesson reagent with no significant effect on the yield of **2a**. Therefore, the optimized conditions selected for thioamides **2a** synthesis were amide **1a** (1.0 mmol) and Lawesson reagent (0.6 mmol) at 80 ^{O}C without solvent.

Encouraged by these results, we next studied the substrate scope of this reaction. Thioamides were synthesized in good to excellent yields under the optimized reaction conditions. Both electron-donating and electron-withdrawing groups are compatible for this reaction. It was found that electron-donating substituents required longer reaction time, as the electron-donating substituent amide decreased the electrophilic character of amide. The electron-withdrawing substituent-containing amides required a shorter reaction time than electron-donating substituent-containing amides. Notably, the reaction of heterocyclic amides, such as pyridine-2-thiocarboxamide and thionictoniamide, proceeded smoothly to provide the thioamide in moderate yields. The scope of the established methodology was also evaluated with various secondary/tertiary amides and nitriles derivatives for obtaining thioamide products. The outcomes showed favorable results with good yield values.

Chapter 5 describes a simple and environmentally friendly, efficient, and practical one-

pot, two-step synthesis of 1,2,4-thiadiazoles from primary amides with Lawesson reagent (LR) and *tert*-butyl hydrogen peroxide (TBHP) as an oxidizing agent in solvent-free conditions. The broad substrate scope, excellent functional group tolerance in mild and metal-free conditions, quick conversion, and excellent yields are essential features of this methodology (**Scheme D**).



Scheme D

At the outset, in order to obtain the maximum yield of the symmetrical 3,5- diphenyl-1,2,4-thiadiazole 3a, the main efforts were directed towards the best reaction conditions for synthesis **3a**. Initially, we selected benzamide **1a**, Lawesson reagent, and TBHP as model substrates to optimize the reaction conditions for the synthesis of **3a**. The effects of different parameters, including reaction medium, molar ratio of oxidant, and temperature, were examined on the model reaction. In search of optimal conditions, first, the reaction was performed with benzamide **1a** (1.0 mmol), Lawesson reagent (0.6 mmol), and 1.5 equiv. TBHP was in a one-pot single-step manner in toluene for 1 h at its refluxed temperature, but it was unsuccessful. Then, we moved from a one-step multi-component protocol to a one-pot, two-step strategy. In the first step of this protocol, benzamide **1a** (1.0 mmol) and Lawesson reagent (0.6 mmol) were used as model substrates for the preparation

of the intermediate thiobenzamide **2a.** This reaction mixture was refluxed in toluene for 1 h, and the conversion to the thiobenzamide **2a** was monitored by TLC; in the second step, the reaction mixture was allowed to cool down to room Reaction temperature, then TBHP was added to it and stirred for 30 min at rt. Gratifyingly, the desired product, 3,5-diphenyl-1,2,4-thiadiazole **3a,** was obtained in 50% yield. Encouraged by this result, we have tested polar aprotic solvents THF, dichloromethane, and acetonitrile under the same reaction conditions giving the product **3a** in 30-50% yield. Then we examined polar protic solvents like ethanol, methanol, and water, but very unfortunately, amide **1a** did not convert into the thioamide **2a,** so we failed to proceed for the second step to give product **3a.**

In order to improve the yield of the product, we moved to solvent-free conditions and maintained the green chemistry principles in organic synthesis reactions. In the first step of the model reaction, benzamide **1a** (1.0 mmol) and Lawesson reagent (0.6 mmol) was heated at 60 ^{o}C under solvent-free conditions for 60 min gave intermediate **2a,** and in the second step, the reaction mixture was allowed to cool at room temperature then TBHP was added to it and stirred for 3 min at rt, gave the desired product 3,5-diphenyl-1,2,4-thiadiazoles **3a** in 65% yield.

Thereafter, the first step of the reaction was carried out at higher temperatures 80^{o}, and 100 ^{o}C. Interestingly, the reaction at 80 ^{o} C temperature with LR (25 min) and 1.5 equiv. TBHP, under solvent-free conditions, was driven to completion with the desired product **3a** to a maximum yield of 92% in a total time of 3 min. The high reaction rate may be due to the increased concentration of the reactants in solvent-free conditions. Further, the increase

in reaction temperature does not show any considerable change in the yield of the product. Next, the different molar ratios of TBHP (1.0, 2.0, 4.0) were also tested; the best result was obtained with 1.5 equiv of TBHP. Thus, the optimized reaction conditions are primary amide **1a** (1.0 mmol), Lawesson reagent (0.6 mmol) at 80 ^{o}C, and TBHP (1.5 mmol) at room temperature under solvent-free conditions.

To broaden the scope of this one-pot, two-step protocol, a series of different primary aromatic/heteroaromatic and aliphatic amides with distinct functionalities were utilized to synthesize a variety of 1,2,4-thiadiazole. Primary aromatic amide, with electron-donating groups like (methyl, tert-butyl, amine, and methoxy) and electron-withdrawing groups as (4-F, Cl, Br,), (3-Cl, Br), and (2-Cl, Br) were effectively resulting the desired products in good yields. Furthermore, the strongly electron-withdrawing groups, such as trifluoromethyl and nitro groups these substrates also underwent a reaction smoothly and yielded the desired products in good yields. Surprisingly, heteroaromatic amides, such as nicotinamide, nicotinamide, thiophene-2-carboxamide, and furan-2-carboxamide, also participated successfully in this reaction, furnishing good yields. Additionally, 1-naphthyl benzamide was subjected to the same conditions and successfully yielded 3,5-(1,1-dinaphthyl)- 1,2,4-thiadiazoles with an 85% yield. To explore the versatility of the reaction, we investigated its compatibility with aliphatic amides, which also underwent smoothly, resulting in the formation of products listed as having good yields.

Thus, our thesis importance is to develop some efficient and greener methodologies for the synthesis of some biologically active nitrogen and sulfur-containing compounds via conventional as well as non-conventional methods, such as renewable energy sources and solvent-free methods, which may make an encouraging contribution to the development of the green and clean chemistry.