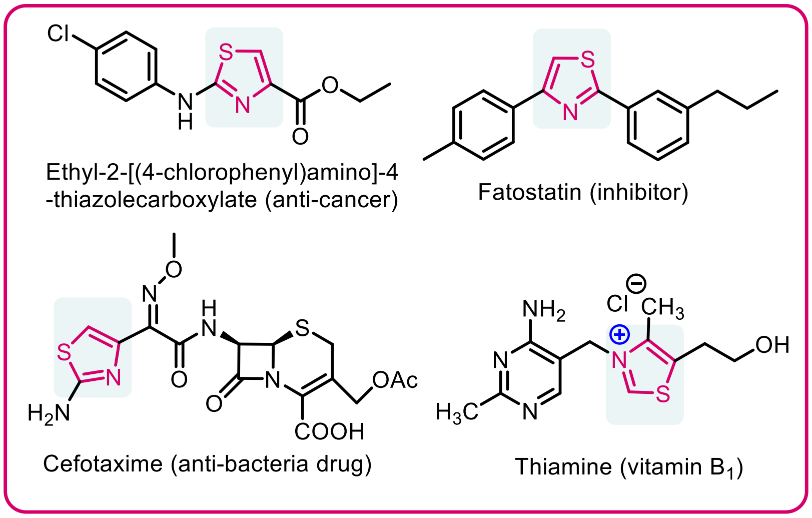
Chapter 3

Visible-light-induced C-S bond formation in the synthesis of 2,4-disubstituted thiazoles through cascade difunctionalization of acetophenone: A greener approach

3.1 Introduction

Visible light has emerged as a valuable and indispensable tool for organic compound formation due to its unique characteristics and numerous advantages [1]. Unlike traditional thermal methods that often require high temperatures and harsh conditions, visible-light-mediated reactions can occur under mild and ambient conditions, making them more environmentally friendly and energy-efficient [2]. Additionally, visible light is abundantly available from natural sources, such as the sun, offering a sustainable and cost-effective alternative to conventional energy sources [3]. Thus, visible light enables the development of greener and more sustainable synthetic processes. Furthermore, visible light possesses lower energy than ultraviolet light, which reduces the risk of unwanted side reactions and enhances the selectivity of the reactions [4, 5]. Its compatibility with a wide range of organic molecules makes it a versatile tool for functional group transformations, enabling the construction of complex and diverse chemical structures [6]. The development of visible-light-responsive photocatalysts and photoredox catalysts has further expanded the scope of visible-light-mediated organic transformations, unlocking new possibilities for synthesizing valuable compounds and facilitating the progress of synthetic chemistry in a more efficient, environmentally conscious, and sustainable manner [7].

In a photo-induced organic synthesis chemical process, light functions as a reagent to speed up the conversion of a compound [8]. Heterocycles containing thiazole structures are special five-membered heterocyclic rings containing sulfur and nitrogen [9, 10]. Thiazole is a precious and synthetically important framework known for its diverse biological activities [11-13]. The synthesis of phenyl thiazole compounds has garnered substantial interest in therapeutic science due to their potential pharmacological importance. These compounds have demonstrated potent and noteworthy biological effects [14, 15] similar to various existing drugs with well-established uses.


Ethyl-2-[(4-chlorophenyl)amino]-4-thiazolecarboxylate (anti-cancer)

Fatostatin (inhibitor)

Cefotaxime (anti-bacteria drug)

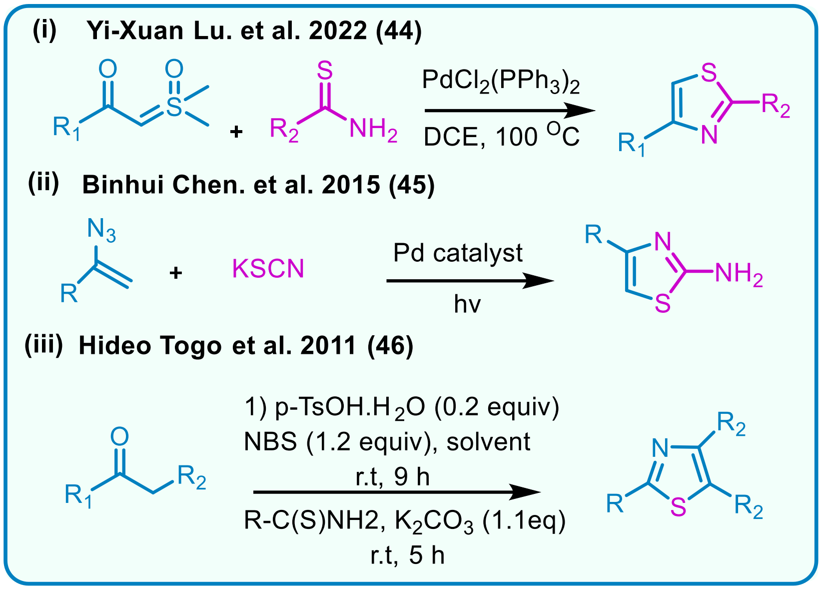
Thiamine (vitamin B_1)

Figure 3.1 Examples of biologically active thiazoles derivatives.

For instance, they exhibit properties akin to anti-inflammatory drugs like Meloxicam [16], anticancer drugs like dasatinib [17, 18], antiparasitic drugs like nitazoxanide [19], pesticide drugs like thiabendazole [20], antimicrobial drugs like sulfathiazole [21], antifungal drugs like abafungin [22, 23], antineoplastic drugs like guineamide [24, 25], broad-spectrum third-generation cephalosporin antibiotics [26], anti-bacteria drugs like cefotaxime, inhibitors like fatotatin, vitamin B_1 thiamine and antiulcerogenic drugs like famotidine [27]. Consequently, thiazole derivatives warrant thorough biological investigations to assess their potential applications in various pharmacological fields [28] (**Figure 3.1**). It may be more efficient to build heterocycles using chemicals that contain sulfur. Numerous natural substances contain organosulfur compounds, which have essential uses in batteries [29], semiconductors, and medicine. Among them, sulfurylide, which includes a sulfur cation and a carbanion, is an effective reagent in organic sulfur compounds [30, 31]. It has been extensively employed in numerous fields due to its straightforward application, safety, and mild reaction conditions. Foremost, sulfur ylide serves as an active framework in drug synthesis. Wang et al. [32] reported asymmetric decarboxylation [4+1] cycloaddition using sulfur ylide with good yields and high selectivity. Fourthly, Yang et al. developed a novel technique for C-C and C-H insertion in the area of photochemistry [33, 34], which could also carry out photochemical rearrangement processes.

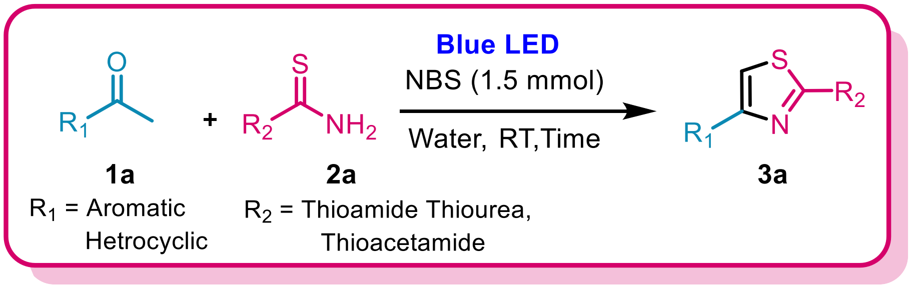
Thus, this imperative ring framework keeps on taking into consideration the medicinal chemists, and a new synthetic way for thiazole rings is being explored. The hantzsch synthesis, which involves [3+2] condensation of α-halo ketones [35] (C-C two atoms unit) with various compounds having an SCN three atoms unit (e.g., thioamides, thioureas, thiosemicarbazides, ammonium dithiocarbamate, and their derivatives) [36, 37], is the most popular of the many synthetic methods reported to achieve thiazole derivatives.

Alkyl, aryl, or heterocyclic substituents can be added to any of the 2-,4-, or 5-positions of the thiazole ring by carefully selecting the reactants [38, 39]. In recent years, a series of oxidative systems, such as HX/ DMSO [40], $KI/NH_4NO_3/H_2SO_4/O_2$ [41], I_2/PTSA/O_2/DMSO [42], $CuCl_2/H_2O$ [43], and $(CH_3)_3SiX-KNO_3$ [33], have been disclosed.



Scheme 3.1. Some previous methods for the synthesis of 2,4-disubstituted thiazoles.

In 2022, Lu and co-workers presented 2,4-diphenyl thiazole synthesis by the reaction of sulfoxonium ylide and thiobenzamide under the catalysis of palladium (**Scheme 3.1, i**) [44]. In 2015, B. Chen and Y. Yu reported the reaction of α-azidostyrene and potassium thiocyanate with $Pd(OAc)_2$ in n-propanol to synthesize 4-phenyl-2-aminothiazole (**Scheme 3.1, ii**) [45]. In particular, Togo and co-workers successfully realized the α-bromination of various ketones by employing NBS in an aqueous medium, which proved to be a highly efficient, environmentally safe, and economical process. (**Scheme 3.1, iii**) [46]. The use of hazardous and corrosive materials and expensive reagents or catalysts, the need for high temperatures, the isolation of lachrymatory α-halo ketones, and low yields are just a few drawbacks of these methods [47]. As a result, there is still room for the development of novel and environmentally friendly syntheses. Due to benefits such as straightforward reaction conditions, environmental friendliness, cost-effectiveness, reduction or elimination of by-products, regioselective product formation, improved yields, purification as a final step, and decreased use of organic solvents, visible-light promoted strategies have attracted a lot of attention in recent years.



1.Renewable energy source (blue LED), 2.Oxidative path way, 3.Cost effective
4.Reaction at room temp. (30-35 ^{o}C), 5.Reaction in water (as a green solvent)

Scheme 3.2 A catalyst-/additive-free photocatalytic method.

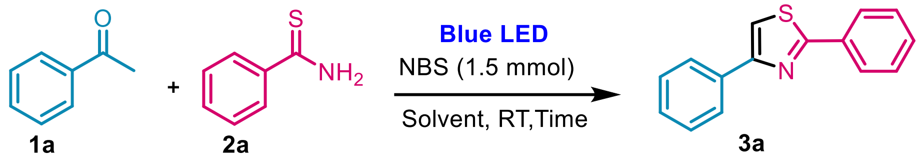
Herein, we wish to report visible light-assisted C-S bond formation in an aqueous medium, followed by a one-pot synthesis of 2,4-disubstituted thiazoles from methyl aryl ketones and thioamide using NBS as a brominating reagent (**Scheme 3.2**).

3.2 Results and Discussion

3.2.1 Optimization of the Reaction Conditions

Initially, we commenced our strategy for synthesizing 2,4-disubstituted thiazoles **3** from acetophenone **1a**, NBS as a brominating reagent, and thiobenzamide **2a**, which was selected as a model reaction. To optimize the reaction conditions under visible light (15 W blue LED of 450 nm) irradiation at room temperature, using Eosin Y (2 mol**%**) as a photocatalyst in water as a solvent, we got 75% yield of our desired product **3a** in 60 min (**Table 3.1 entry 1**). The yield of the product with Eosin Y encouraged us to optimize various polar and non-polar solvents, such as ethanol, DCM, acetonitrile, THF, toluene and a green solvent dimethyl carbonate (DMC), to see the effect on the reaction efficiency but provided only 35-66% yields (**Table 3.1, entries 2-8**). 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 (**Table 3.1, entries 9-11**). Then, we tried the reaction in a catalyst-free condition in water, and surprisingly, 90% yield of the product was obtained in only 30 minutes (**Table 3.1, entry 12**). This may be due to the separation process of photocatalysts or the unstability of the product in the presence of photocatalysts. After that, the reaction was carried out in the dark, but we didn’t get any yield of the product showing the significance of light irradiation for this reaction (**Table 3.1 entry 13**). The reaction was also carried out by the conventional method, refluxing in water without blue light, which gave only 70% yield of the product (**Table 3.1, entry 14**).

Table 3.1. Initial optimization of the reaction conditions for the synthesis of thiazole **3a**[a]

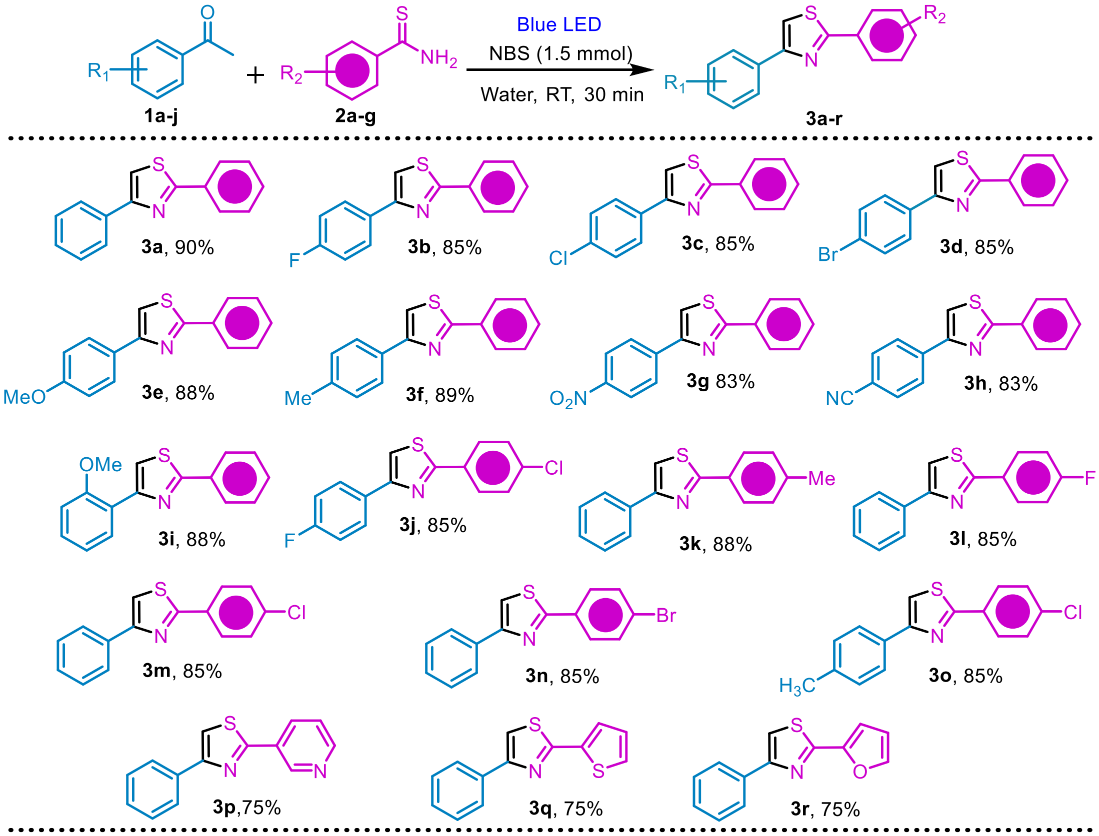


S.N	Catalyst (mol%)	Solvent	Time (h)	Light source	Yields (%)[b]
1	Eosin Y (2)	Water	1 (h)	Blue light	75
2	Eosin Y (2)	Ethanol	1 (h)	Blue light	60
3	Eosin Y (2)	H_2O:EtOH(1:1)	1 (h)	Blue light	66
4	Eosin Y (2)	DCM	1 (h)	Blue light	35
5	Eosin Y (2)	Acetonitrile	1 (h)	Blue light	40
6	Eosin Y (2)	THF	1 (h)	Blue light	45
7	Eosin Y (2)	DMC	1 (h)	Blue light	35
8	Eosin Y (2)	Toluene	1 (h)	Blue light	Trace
9	Rose Bengal (2)	Water	1 (h)	Blue light	41
10	Acridine red (2)	Water	1 (h)	Blue light	46
11	Rhodamine B (2)	Water	1 (h)	Blue light	30
12	-	Water	30 min	Blue light	90
13	-	Water	30 min	Dark	n.r
14[c]	-	water	30 min	-	70
15	-	Water	30 min	Green light	60
16	-	Water	30 min	Purple light	55
17	-	Water	30 min	White light	30

[a] **Reaction condition**: Acetophenone **1a** (1.0 mmol), thiobenzamide **2a** (1.2 mmol), catalyst (2 mol %), solvent (3 ml), Blue LED (30 min) at room temperature. [b] Isolated yield.

Subsequently, various light sources were also investigated, but the yield was unsatisfactory (**Table 3.1, entries 15-17**). So the optimized conditions for the synthesis of 2,4-disubstituted thiazole **3a** are acetophenone **1a** (1.0 mmol), NBS (1.5 mmol), and thiobenzamide **2a** (1.2 mmol), water as a solvent under 15 W blue LED irradiation. Product **3a** was characterized by spectral data (^{1}H, ^{13}C NMR, HRMS) and confirmed by comparing the data with those reported.

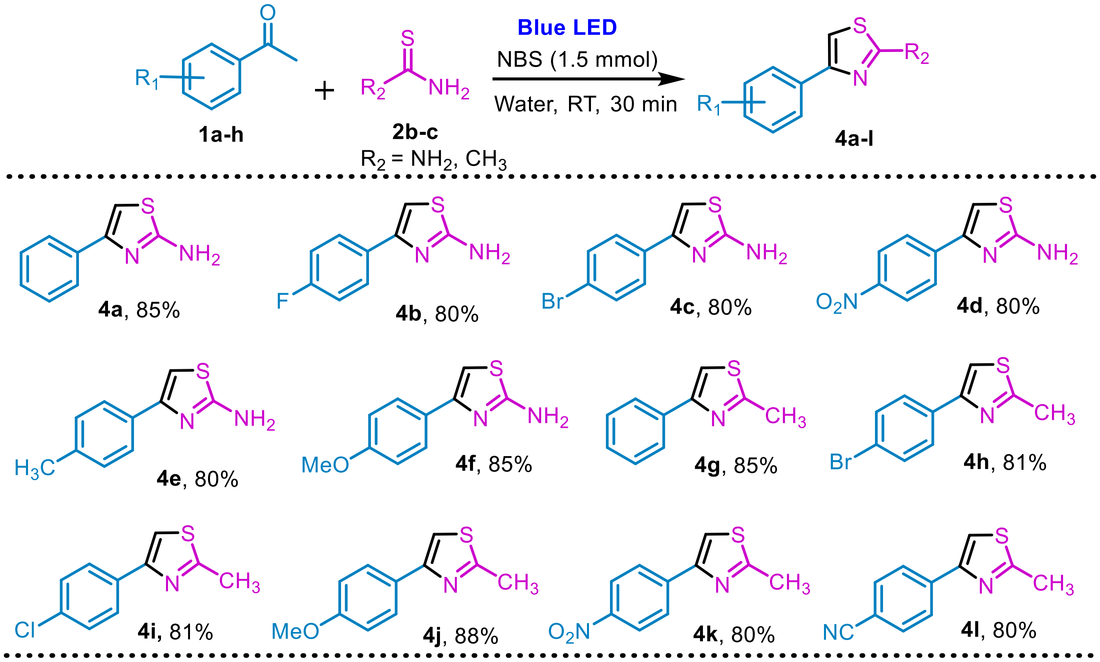
Table 3.2. Substrate scope for synthesizing 2,4-disubstituted thiazole from methyl aryl ketone and aromatic thioamide.



Reaction condition: Methyl aryl ketone (1.0 mmol), thioamide (1.2 mmol), solvents (3 ml) at room temperature for 30 min, and irradiation under blue LED.[b] Isolated yield.

After optimizing the reaction conditions at hand, we focused on studying the scope of this reaction with various methyl aryl ketones and thioamides (**Table 3.2**). Both electron-withdrawing (F, Cl, Br, NO_2, and CN), and electron-donating (OMe, Me) groups on the phenyl ring of methyl aryl ketones gave (**3b-i**) in moderate to good (83-89%) yields. Substituted thioamides, such as methyl and halogen thioamides, reacted with methyl aryl ketones and gave the corresponding products (**3j-o**) in good yields, and heterocyclic thioamides gave **3p** and **3r** in moderate yields (**Table 3.2**).

Table 3.3. Substrate scope for the synthesis of 2,4-disubstituted thiazole from methyl aryl ketone and aliphatic thioamide.



Reaction condition: Methyl aryl ketone (1.0 mmol), thiourea/thioacetamide (1.2 mmol), solvents (3 ml) at room temperature for 30 min, and irradiation under blue LED. [b] Isolated yield.

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, and the results were summarized in (**Table 3.3**). In order to evaluate the electronic influence of substituents on the aromatic ring of acetophenone, a series of substituted acetophenone (**1a-h**) were examined. The results showed that in the case of electron-withdrawing groups (F, Br, and NO_2), the corresponding products were obtained in moderate to good yields of 80%. In contrast, the electron-donating groups (Me and OMe) provided good to excellent yields 80% and 85% of the corresponding products. To further expand the scope of the aryl ketone with thiourea and thioacetamide were also investigated, and the desired products were obtained in good yields of 81-88%. 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 in green, catalyst-free, and base-free conditions at room temperature.

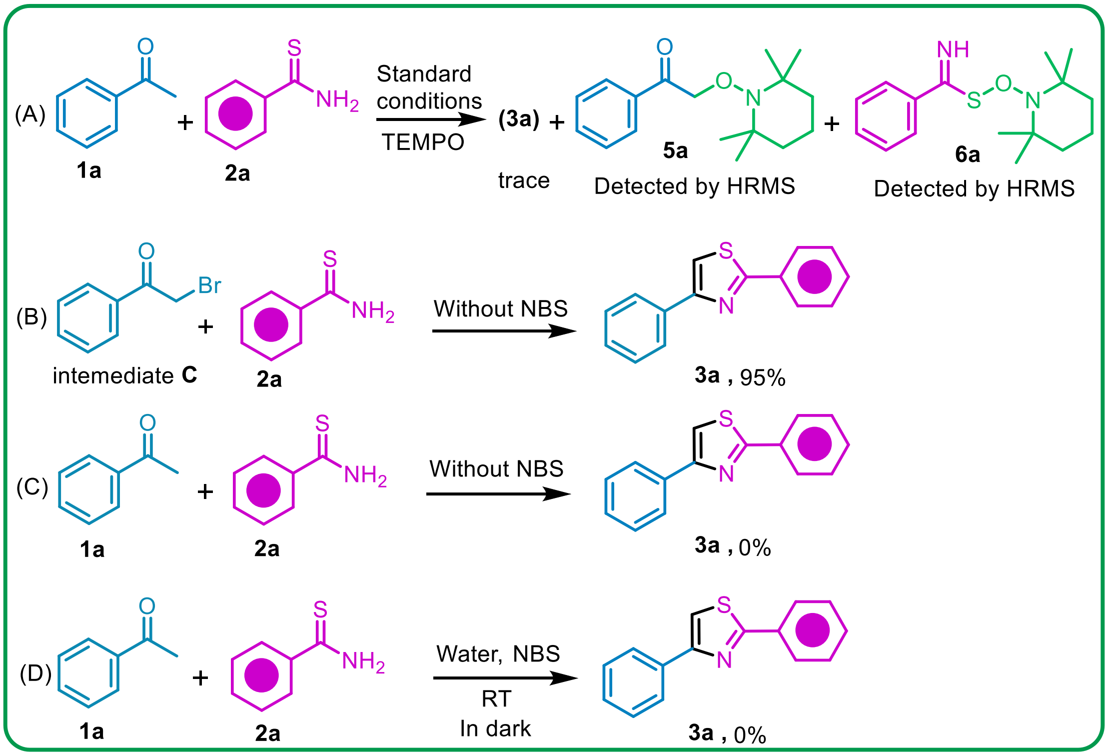
3.2.2 Gram-scale synthesis protocol for 2,4-disubstitued thiazole (3a)

Scheme 3.3 Synthesis of **3a** product on gram-scale.

To assess the feasibility of the synthetic application of a well-established approach for 2,4-disubstituted thiazole **3a** that is aided by visible light, the experiment was conducted on gram scale using methyl aryl ketone **1a** (5.0 mmol, 1.0 equiv.), NBS (7.5 mmol, 1.5 equiv.), thioamide **2a** (6.0 mmol, 1.2 equiv.) standard conditions (**Scheme 3.3**). The experiment was carried out at room temperature, with water as a green solvent for 30 min, and the progress was monitored with TLC. The precipitate obtained was filtered and washed with ethanol after the completion of the reaction. The desired product obtained in good yields after recrystallization using ethanol (**3a,** 87%). The experimental work showed a robust and acceptable gram-scale method for the synthesis of 2,4-substituted thiazole. The results showed that visible light could be used as an efficient and renewable light source in this strategy.

3.3 Optimized Experiments and Mechanistic Studies

In order to establish the reaction mechanism, some optimized experiments were performed under the optimized reaction conditions (**Scheme 3.4**). The optimized reactions were carried out between methyl aryl ketone and thioamide without a catalyst to provide the product **3a** (**Table 3.1, entry 12**). When the reaction was performed in the presence of the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-yl) (2.0 equiv.) (**Scheme 3.4 A**), less than 10% yield of the desired product was obtained, which indicates that the formation of 2,4-disubstituted thiazole involves a radical mechanistic pathway. The control reaction was also carried out between 2-bromoacetophenone and thioamide without a catalyst, giving the product **3a** in 95% yields (**Scheme 3.4 B**). Further, the reaction was carried out with acetophenone **1a** and thioamide **2a** in the absence of NBS, and we didn’t get any yield; this result shows that NBS works in the first step (**Scheme 3.4 C**). After that, the control reaction was executed between 2-bromoacetophenone thioamide under dark conditions, which failed to give the product (0% yield) (**Scheme 3.4 D**).



Scheme 3.4 Optimiized experiments.

3.3.1 UV-Vis Absorption Experiment

After evaluating the sensitivity and reproducibility of the substrate scope, we moved our attention toward the mechanism of the reaction and conducted several mechanistic investigations. The UV-visible spectra of reactants (**1a** and **2a),** and reaction mixtures (**1a+2a**) were observed (**Figure 3.2**). The finding showed that, except for the reactants, the reaction mixture without photocatalyst absorbs blue light.

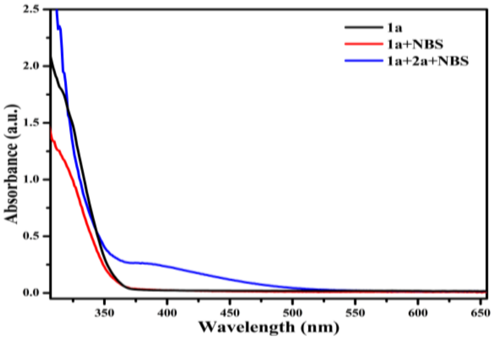
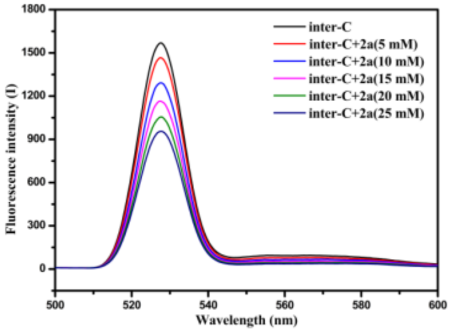


Figure 3.2 UV-Vis absorption spectra.

3.3.2 Stern-Volmer Fluorescence Quenching Experiments

Next, we carried out Stern-Volmer experiments between **1a** and **2a**, and no quenching effect was observed. A quenching effect was observed when we carried out the same experiment with the isolated intermediate C (α-bromo ketone). The results of the stern-volmer experiments showed that intermediate C was successfully quenched by **2a** (**Figure 3.3**).



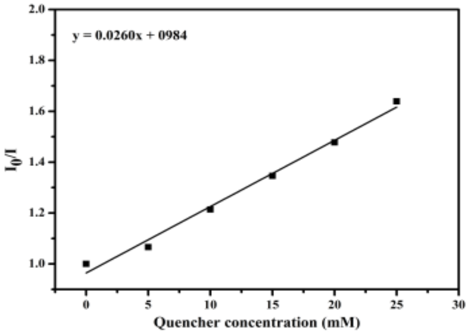


Figure 3.3. The fluorescence emission spectra of **1a** with different concentrations of quencher **2a**. **Figure 3.4** Stern-Volmer plot.

As seen in (**Figure 3.3)**, the quenching effect gets more pronounced as the concentration of **2a** increases. It was discovered that there was a linear relationship between the concentration of **2a** and *I0/I* (*I0* and *I* are the fluorescence intensities prior to and following the addition of **2a**) (**Figure 3.4**).

3.3.3 Light-Dark Cycle Experiment

The outcomes showed that **2a** was an effective quencher of intermediate **C**. The light ON/OFF experiments proved the critical role of blue light (**Figure 3.5**) and excluded the nucleophilic reaction pathway

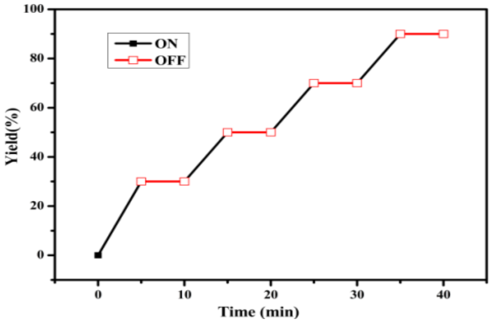
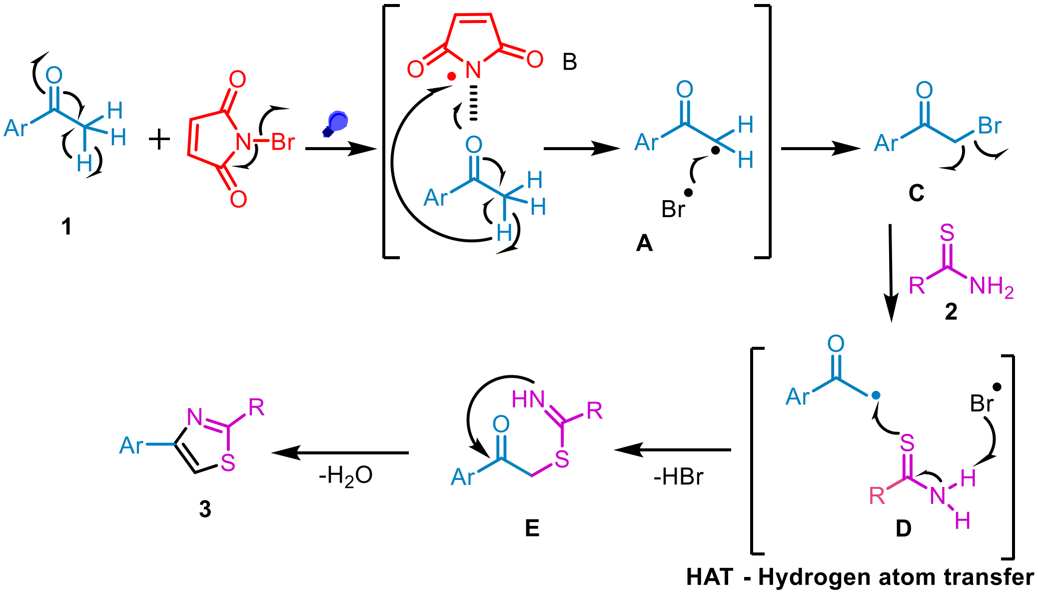


Figure 3.5. Light-dark cycle experiment.

3.4 Plausible Reaction Mechanism

According to the control experiments and literature [49], a possible mechanism was proposed (**Figure 3.6**). First, the methyl aryl ketone and NBS react to generate the radical intermediate **A**, NBS radical **B**, and bromine radical under blue LED at room temperature. The recombination of radical **A** and the bromine radical provides an intermediate **C**, which, after radical dissociation, forms the bromine radical and benzylic radical. These two radicals react with thioamide to form **D** via hydrogen atom transfer. Further, this intermediate **D** undergoes cyclization via the elimination of HBr to form an intermediate **E**. After removing a water molecule, and this intermediate **E** provides the desired product **3**.



Scheme 3.5 Plausible mechanism.

3.5 Conclusions

In conclusion, we developed a visible-light-induced 2,4-disubstituted thiazole from methyl aryl ketone and thioamide in the presence of a green solvent. All the reactions were carried out at room temperature. The advantages of this procedure are photocatalyst and metal-free, mild reaction conditions, operational simplicity, and high yields of the products. Notably, the synthesis of 2-unsubstituted benzothiazoles was also achieved without any difficulty. The mechanistic course of the reaction is clearly justified through control experiments and UV-Vis studies, according to which the reaction proceeds via the formation of a radical pathway between methyl aryl ketone and thioamide. Therefore, it is expected that the metal-free catalyzed reaction of acetophenone can use its advantages to synthesize other heterocyclic compounds, which has very important application prospects.

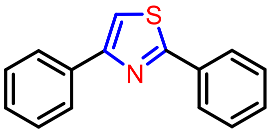
3.6 Experimental Procedures

3.6.1 General procedure for the synthesis of 2,4-disubstituted thiazole 3a-3r & 4a-4l

A 25 ml RB flask equipped with a magnetic stirring bar was charged with methyl aryl ketone **1a** (1.0 mmol), thioamide/thiourea **2a/2b** (1.2 mmol), and solvent (3 ml). The mixture was stirred at room temperature and irradiated with blue LEDs light strips for 30 min under the open air. The progress of the reaction was monitored via TLC. The precipitate obtained was filtered and washed with ethanol after the completion of the reaction. The desired product was obtained in good yields after recrystallization using ethanol.

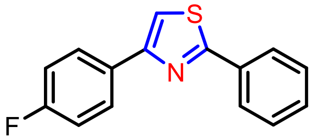
3.7 Analytical data for [3a-3r, 4a-4l]

2,4-diphenyl thiazole (3a)



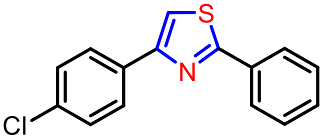
Yield 90%; white solid; m.p. 90 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 8.09 (m, 2H), 8.04 (m, 2H), 7.50-7.48 (m, 6H), 7.47-7.39 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 167.9, 156.3, 134.5, 133.8, 130.1, 128.9, 128.8, 128.2, 126.6, 126.5, 112.6 ppm. HRMS ESI $[M+H]^+$ calculated for $C_{15}H_{11}NS$ 238.0612, found 239.0616.

4-(4-fluorophenyl)-2-phenylthiazole (3b)



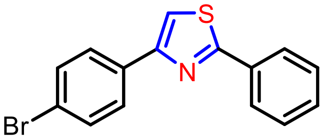
Yield 85%; white solid; m.p. 103-104 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 8.07 (m, 2H), 8.06-8.00 (m, 2H), 7.49-7.46 (m, 3H), 7.40-7.37 (m, 1H), 7.20-7.16 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 168.0, 161.8 (d, J = 248.7 Hz), 155.3, 133.5, 130.8, 130.1 (d, J = 3.7 Hz), 128.9, 128.2 (d, J = 7.6 Hz), 126.6, 115.7 (d, J = 21.4 Hz), 112.2 ppm. HRMS ESI $[M+H]^+$ calculated for $C_{15}H_{10}FNS$ 256.0517, found 257.0520. **^{19}F NMR** 108.9

4-(4-chlorophenyl)-2-phenylthiazole (3c)



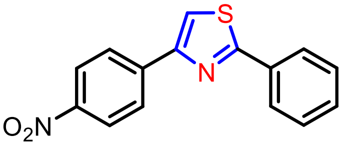
Yield 85%; white solid; m.p. 131 °C;**^{1}H NMR** (500 MHz, $CDCl_3$); δ 8.09-8.08 (m, 2H), 8.04-8.03 (m, 2H), 7.50-7.37 (m, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 168.3, 156.0, 134.6, 133.8, 130.0, 128.9, 128.8, 128.2, 126.6, 126.5, 112.6 ppm. HRMS ESI $[M+H]^+$ calculated for $C_{15}H_{10}ClNS$ 272.0222, found 273.0220.

4-(4-bromophenyl)-2-phenylthiazole (3d)



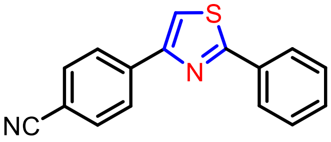
Yield 85%; white solid; m.p. 134-135 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 8.07-8.05 (m, 2H), 7.91-7.89 (m, 2H), 7.60-7.59 (m, 1H), 7.51-7.47 (m, 5H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 168.2, 155.1, 133.6, 133.4, 131.9, 130.2, 128.9, 128.0, 126.6, 122.2, 113.0 ppm. HRMS ESI $[M+H]^+$ calculated for $C_{15}H_{10}BrNS$ 315.9717, found 316.9721.

4-(4-nitrophenyl)-2-phenylthiazole (3e)



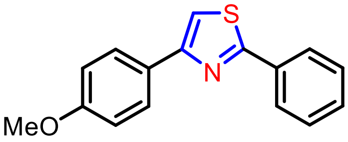
Yield 83%; yellow solid; m.p. 135-136 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 8.32-8.30 (d, J = 8.9 Hz, 2H), 8.18-8.16 (d, *J* = 8.8 Hz, 2H), 8.07-8.05 (d, *J* = 8.8 Hz, 2H), 7.69 (s, 1H), 7.51-7.50 (m, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 168.8, 153.8, 147.3, 140.3, 133.2, 130.6, 129.0, 126.9, 126.7, 124.2, 116.0. HRMS $[M+H]^+$ calculated for $C_{15}H_{10}N_2O_2S$ 283.0463, found 284.0467.

4-(4-cyanophenyl)-2-phenylthiazole (3f)



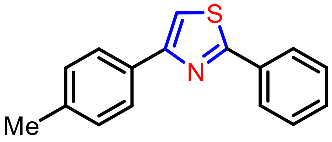
Yield 83%; yellow solid m.p. 135-137 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 8.14-8.12 (d, J = 8.4 Hz, 2H), 8.07-8.05 (m, 2H), 7.76-7.75 (d, *J* = 8.4 Hz, 2H), 7.65 (s, 1H), 7.50-7.49 (m, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 168.7, 154.2, 138.5, 133.3, 132.6, 130.5, 129.0, 126.9, 126.7, 119.0, 115.3, 111.4 ppm. HRMS $[M+H]^+$ calculated for $C_{16}H_{10}N_2S$ 263.0564, found 264.0560.

4-(4-methoxyphenyl)-2-phenylthiazole (3g)



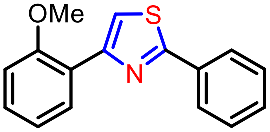
Yield 88%; pale yellow solid; m.p. 115-116 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 8.07-8.05 (d, 2H), 7.97-7.95 (d, 2H), 7.50-7.45 (m, 3H), 7.37 (s, 1H), 7.01-7.00 (d, 2H), 3.89(s, 3H, OCH_3) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 167.7, 159.7, 156.1, 133.9, 130, 129, 129.9, 128.7, 127.8, 126.6, 114.1, 110.9, 55.4 ppm. HRMS $[M+H]^+$ calculated for $C_{16}H_{13}NOS$ 268.0717, found 269.0713.

2-phenyl-4-p-tolylthiazole (3h)



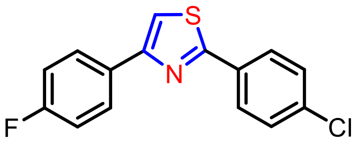
Yield 89%; white solid; m.p. 116 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 8.08-8.06 (d, 2H), 7.93-7.91 (d, 2H), 7.50-7.45 (m, 4H), 7.29-7.26 (m, 2H), 2.43 (s, 3H, CH_3) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 167.7, 156.4, 138.0, 133.9, 131.9, 130.0, 129.4, 128.9, 126.6, 126.4, 111.9, 21.3 ppm. HRMS $[M+H]^+$ calculated for $C_{16}H_{13}NS$ 252.0768, found 253.0764.

4-(2-methoxyphenyl)-2-phenylthiazole (3i)



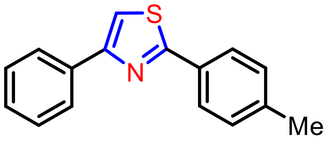
Yield 88%; white solid; m.p. 83 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 8.48-8.46 (d, J = 8.4 Hz, 1H), 8.10-8.08 (d, 2H), 7.99 (s, 1H), 7.51-7.44 (m, 3H), 7.37-7.34 (m, 1H), 7.15-7.12 (m, 1H), 7.06-7.04 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 165.7, 157.0, 152.0, 134.0, 130.3, 129.8, 128.9, 128.9, 126.7, 123.3, 121.0, 117.1, 111.1, 55.5 ppm. HRMS $[M+H]^+$ calculated for $C_{16}H_{13}NOS$ 268.0717, found 269.0713.

2-(4-chlorophenyl)-4-(4-fluorophenyl)-thiazole (3j)



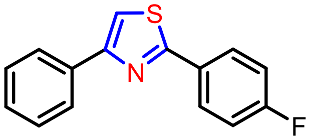
Yield 85%; white solid m.p. 125-127 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 8.00-7.97 (m 4H), 7.47-7.44 (m 4H), 7.18-7.14 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 166.7, 163.8, 161.9, 155.5, 136.0, 132.1, 130.6, 129.1, 128.2, 127.9, 115.8, 112.4 ppm. HRMS $[M+H]^+$ calculated for $C_{15}H_9ClFNS$ 290.0128, found 291.0132.

4-phenyl-2-(4-methylphenyl) (3k)



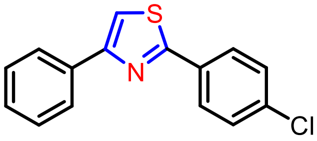
Yield 88%; white solid m.p. 124-125 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); *δ* 8.03 (d, *J* = 7.4 Hz, 2H), 7.97-7.96 (d, *J* = 8.1 Hz, 2H), 7.49-7.46 (m, 3H), 7.39-7.38 (t, *J* = 7.4 Hz, 1H), 7.30-7.28 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); *δ* 168.1, 156.2, 140.3, 134.6, 131.2, 129.6, 128.7, 128.1, 126.5, 126.4, 112.2, 21.5 ppm. HRMS $[M+H]^+$ calculated for $C_{16}H_{13}NS$ 252.0768, found 253.0764.

4-phenyl-2-(4-flurophenyl) (3l)



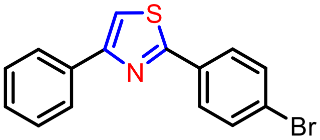
Yield 85%; white solid mp 117-118 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); *δ* 8.08-8.00 (m, 4H), 7.49-7.46 (m, 3H), 7.40-7.37 (m, 1H), 7.20-7.16 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$, ppm); *δ* 166.7, 164.9 (d, *J* = 250.7 Hz), 156.4, 134.4, 130.1 (d, *J* = 3.7 Hz), 128.8, 128.6 (d, *J* = 8.8 Hz), 128.3, 126.4, 116.1, 115.9 (d, *J* = 22.7 Hz); HRMS $[M+H]^+$ calculated for $C_{15}H_{10}FNS$ 256.0517, found 257.0513

4-phenyl-2-(4-chlorophenyl) (3m)



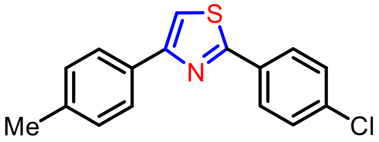
Yield 85%; white solid m.p. 110 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); *δ* 8.02-8.00 (m, 4H), 7.50-7.40 (m, 5H), 7.40-7.38 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); *δ* 166.5, 156.5, 136.0, 134.3, 132.3, 129.2, 128.8, 128.3, 127.8, 126.5, 112.8 ppm. HRMS $[M+H]^+$ calculated for $C_{15}H_{10}ClFNS$ 272.0222, found 273.0225.

4-phenyl-2-(4-bromophenyl) (3n)



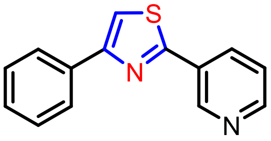
Yield 85%; white solid m.p. 103-104 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 8.07-8.05 (m, 2H), 7.91-7.89 (m, 2H), 7.60-7.59 (m, 2H), 7.51-7.50 (m, 3H), 7.48-7.47 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 168.2, 155.2, 133.6, 133.4, 131.9, 130.2, 128.9, 128.0, 126.6, 122.2, 113.0 ppm. HRMS $[M+H]^+$ calculated for $C_{15}H_{10}ClFNS$ 315.9717, found 315.9714.

2-(4-chlorophenyl)-4-(p-tolyl)-thiazole (3o)



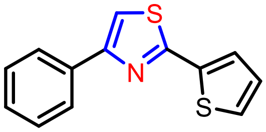
Yield 85%; white solid, m.p. 164-165 °C, **^{1}H NMR** (500 MHz, $CDCl_3$); δ 8.01-7.99 (m, 2H), 7.91-7.89 (d, *J* = 1.8 Hz, 2H), 7.46-7.45 (m, 3H), 7.29-7.27 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 166.4, 156.6, 138.2, 135.9, 132.3, 131.6, 129.5, 129.1, 127.8, 126.4, 112.1, 21.3 ppm. HRMS $[M+H]^+$ calculated for $C_{16}H_{12}ClNS$ 286.0378, found 287.0381.

4-phenyl-2-(pyridin-3-yl)-thiazole (3p)



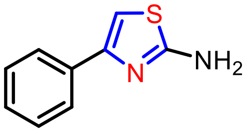
Yield: 75%; Pale Yellow solid, m.p. 268-269 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 8.90-8.88 (d, J = 1.5 Hz, 1H), 8.75 (dd, *J* = 5.0 Hz, 1H), 7.95-7.91 (dd, *J* = 8.0 Hz, 5H), 7.52-7.49 (dd, *J* = 8.5 Hz, 1H), 7.19-7.18 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 164.3, 156.9, 150.6, 147.6, 134.1, 133.8, 129.9, 128.8, 128.5, 126.5, 123.8, 113.3 ppm. HRMS $[M+H]^+$ calculated for $C_{14}H_{10}N_2S$ 239.0564, found 240.0560.

4-phenyl-2-(thiophen-2-yl)-thiazole (3q)



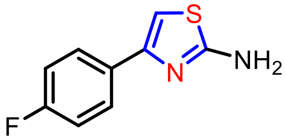
Yield 75%; colourless oil, **^{1}H NMR** (500 MHz, $CDCl_3$); *δ* 8.43-8.41 (m, 2H), 8.09-8.07 (m, 2H), 7.91-7.89 (m, 1H), 7.56-7.55 (m, 3H), 7.52-7.43 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); *δ* 161.2, 156.5, 137.2, 134.3, 129.2, 128.8, 128.3, 127.8, 126.5, 112.9 ppm. HRMS $[M+H]^+$ calculated for $C_{13}H_9NS_2$ 244.0176, found 245.0172.

4-phenylthiazol-2-amine (4a)



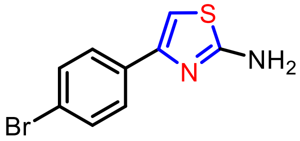
Yield 85%; pale yellow solid; m.p. 150-151 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); *δ* 7.81 (m, 2H), 7.42-7.39 (m, 2H), 7.33-7.31 (m, 1H), 6.75 (s, 1H), 4.12-4.11 (s, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); *δ* 167.2, 151.4, 134.7, 128.6, 127.7, 126.0, 102.9, ppm. HRMS $[M+H]^+$ calculated for $C_9H_8NS_2$ 177.0408, found 178.0404.

4-(4-flurophenyl)-thiazol-2-amine (4b)



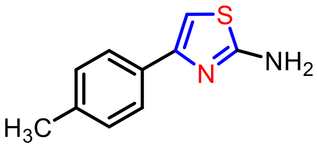
Yield 80%; White Solid; m.p. 102-103 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); *δ* 7.76-7.72 (m, 2H), 6.95-6.92 (m, 2H), 6.61 (s, 1H), 4.98 (s, 2H) ppm. **^{13}C NMR** (126 MHz $CDCl_3$); *δ* 167.3, 163.5, 161.5, 150.2, 130.8, 127.7, 127.7, 115.6, 115.4, 102.4 ppm. HRMS $[M+H]^+$ calculated for $C_9H_7FN_2S$ 195.0313, found 196.0320.

4-(4-bromophenyl)-thiazol-2-amine (4c)



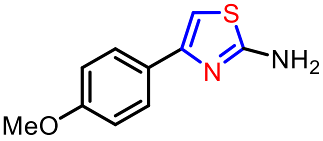
Yield 80%; white solid; m.p. 182-183 °C; **^{1}HNMR** (500 MHz, $CDCl_3$); δ 7.67-7.66 (m, 2H), 7.52-7.51 (m, 2H), 6.74 (s, 1H), 5.11 (brs, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 167.3, 150.2, 133.6, 131.7, 127.6, 121.6, 103.4 ppm. HRMS $[M+H]^+$ calculated for $C_9H_7BrN_2S$ 254.9513, found 255.9516.

4-(4-methylphenyl)-thiazol-2-amine (4d)



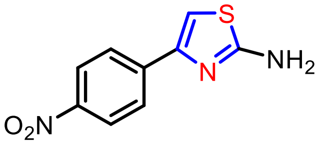
Yield 80%; white solid, m.p. 150-151 °C; **^{1}H NMR** (500 MHz,$CDCl_3$); δ 7.69-7.68 (d, *J* = 8.0 Hz, 2H), 7.21-7.20 (d, *J* = 8.5 Hz, 2H), 6.69 (s, 1H), 5.11 (brs, 2H), 2.38 (s, 3H) ppm.**^{13}C NMR** (126 MHz, $CDCl_3$); δ 167.2, 151.4, 137.5, 131.9, 129.3, 125.9, 102.1, 21.2 ppm. HRMS $[M+H]^+$ calculated for $C_{10}H_{10}N_2S$ 191.0565, found 192.0569.

4-(4-methoxyphenyl)-thiazol-2-amine (4e)



Yield 85%; brown solid, m.p: 199-200 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 7.91-7.89 (d, *J* = 8.7 Hz, 1H), 7.77-7.76 (d, *J* = 6.0 Hz, 1H), 7.69-7.67 (m, 1H), 7.58-7.56(m, 1H), 6.91 (m, 1H), 5.03 (brs, 2H) 4.12 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$); δ 165.8, 159.6, 155.0, 127.8, 127.7, 114.3, 98.1, 55.4 ppm. HRMS $[M+H]^+$ calculated for $C_{10}H_{10}N_2OS$ 207.0513, found 208.0517.

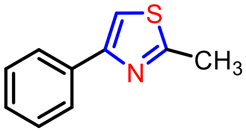
4-(4-nitroyphenyl)-thiazol-2-amine (4f)



Yield 80%; brown solid, m.p: 199-200 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 8.03-8.02 (d, *J* = 8.7 Hz, 2H), 7.68-7.67 (d, *J* = 6.0 Hz, 2H), 6.67 (s, 1H), 4.98 (brs, 2H). **^{13}C NMR** (126

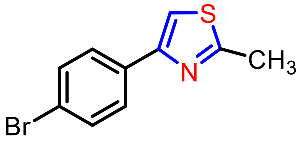
MHz, $CDCl_3$); δ 167.2, 148.1, 143.8, 138.8, 127.3, 127.2, 126.1, 126.0, 107.5 ppm. HRMS $[M+H]^+$ calculated for $C_{10}H_{10}N_2OS$ 222.0259, found 222.0554.

4-phenyl-2-methyl-thiazole (4g)



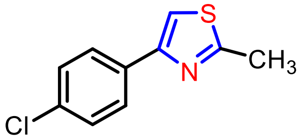
Yield 85%; white solid; m.p. 65-66 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 7.91-7.90 (m, 2H), 7.45-7.42 (m, 2H), 7.36 (m, 1H), 7.33 (m, 1H), 2.80 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 165.9, 155.2, 134.5, 128.8, 128.7, 128.5, 127.9, 126.3, 112.3, 19.3 ppm. HRMS $[M+H]^+$ calculated for $C_{10}H_9NS$ 176.0455, found 177.0452

4-(4-bromophenyl)-2-methyl-thiazole (4h)



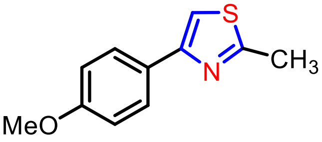
Yield 83%; white solid; m.p. 130-131 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 7.76-7.75 (m, 2H), 7.55-7.54 (m, 2H), 7.33-7.28 (m, 1H), 2.78-2.77 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$); δ 165.2, 154.0, 133.5, 131.8, 127.9, 121.9, 112.7, 19.3 ppm. HRMS $[M+H]^+$ calculated for $C_{10}H_8BrNS$ 253.9560, found 254.9564.

4-(4-chlorophenyl)-2-methyl-thiazole (4i)



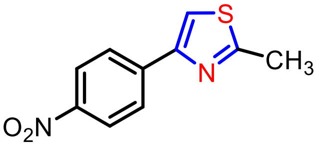
Yield 83%; white solid; m.p. 113 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 7.76-7.75 (m, 2H), 7.55 (s, 2H), 7.33-7.30 (m, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$); δ 166.2, 154.0, 134.1, 133.5, 128.9, 127.9, 112.7, 19.3 ppm. HRMS $[M+H]^+$ calculated for $C_{10}H_8ClNS$ 210.0065, found 211.0062.

4-(4-methoxyphenyl)-2-methyl-thiazole (4j)



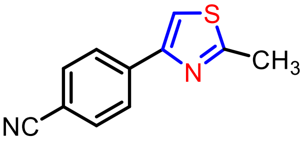
Yield 88%; white solid; m.p. 66-68 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); *δ* 7.83-7.81 (m, 2H), 7.18 (s, 1H), 6.97-6.95 (m, 2H), 3.86 (s, 3H), 2.78 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$); *δ* 165.7, 159.5, 154.9, 127.6, 127.5, 114.1, 110.5, 55.3, 19.3 ppm. HRMS $[M+H]^+$ calculated for $C_{11}H_{11}NOS$ 206.0561, found 207.0565.

4-(4-nitrophenyl)-2-methyl-thiazole (4k)



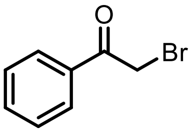
Yield 80%; white solid; m.p. 132-135 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); *δ* 8.36-8.28 (m, 2H), 8.07-8.06 (m, 2H), 7.55 (m, 1H), 2.81 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); *δ* 166.8, 152.7, 147.2, 140.3, 140.0, 126.8, 124.2, 124.0, 115.9, 19.3 ppm. HRMS $[M+H]^+$ calculated for $C_{10}H_8N_2O_2S$ 221.0408, found 222.0404.

4-(4-cyanophenyl)-2-methyl-thiazole (4l)



Yield 80%; white solid; m.p. 134 °C; **^{1}H NMR** (500 MHz, $CDCl_3$); *δ* 8.10-8.00 (m, 2H), 7.82-7.70 (m, 2H), 7.49 (s, 1H), 2.81 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); *δ* 166.8, 153.0, 138.6, 132.6, 126.8, 118.9, 115.2, 111.3, 19.3 ppm. HRMS $[M+H]^+$ calculated for $C_{11}H_8N_2S$ 201.0408, found 202.0411.

2-bromo-1-phenylethan-1-one (Figure 6, Intermediate C)



m.p. 53°C; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 8.02-8.00 (m, 2H), 7.65-7.62 (m, 1H), 7.54-7.51 (m, 2H), 4.49 (s, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$); δ 191.3, 134.0, 133.9, 128.9, 128.9, 30.9 ppm.

3.8 Spectral Data of Few Products

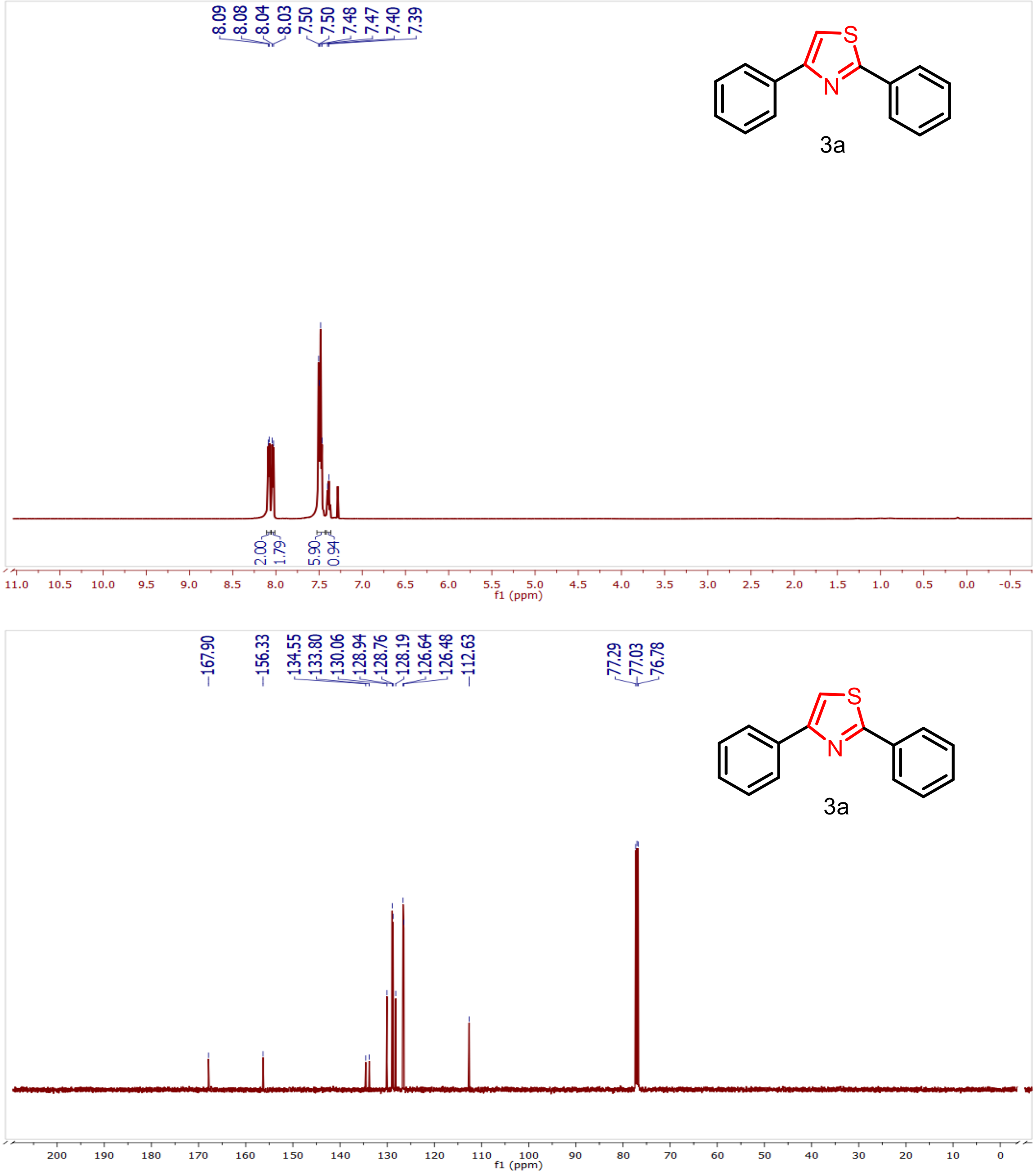


Figure 3.6 ^{1}H & ^{13}C NMR of product **3a**

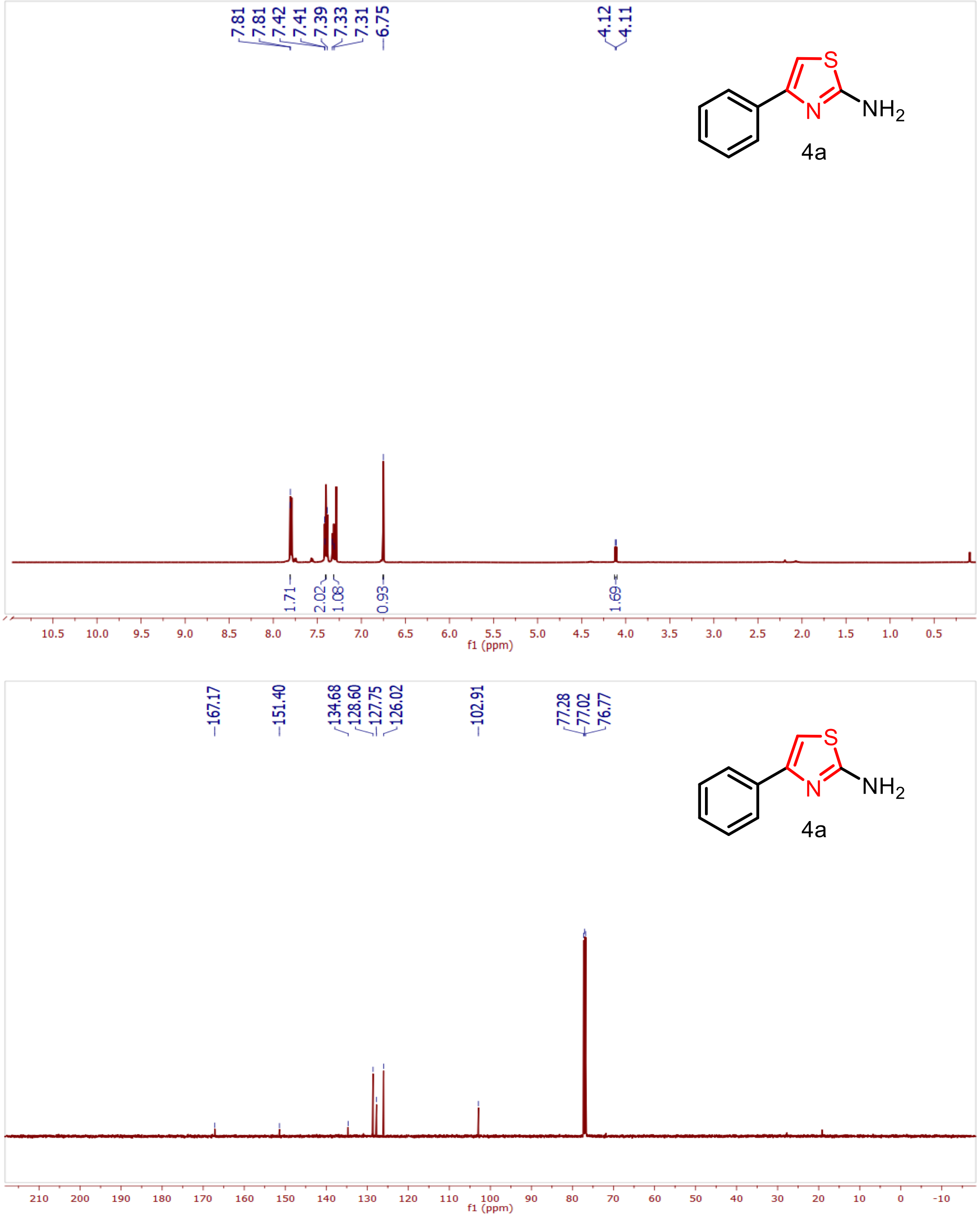
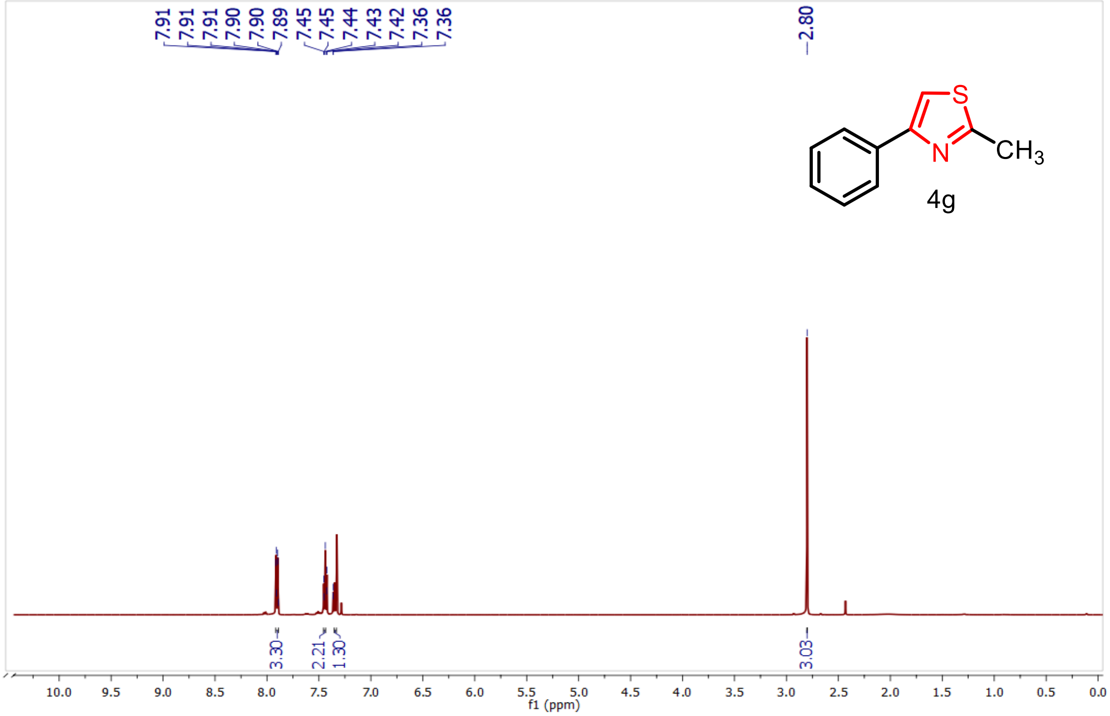


Figure 3.7 ^{1}H & ^{13}C NMR of product **4a**



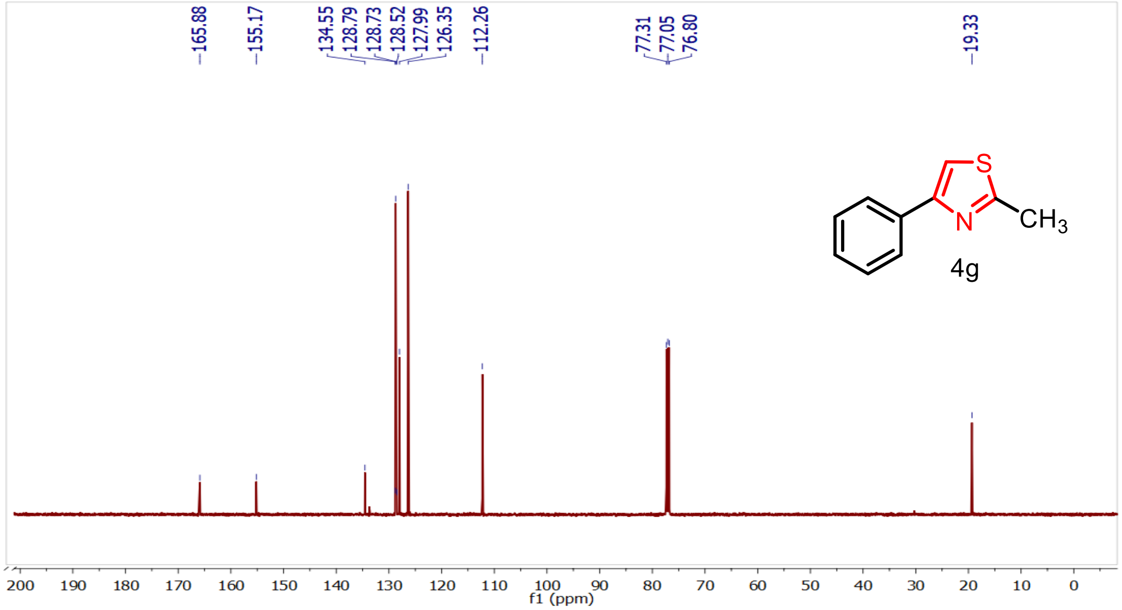


Figure 3.8 ^{1}H & ^{13}C NMR of product **4g**

3.9 HRMS Spectra

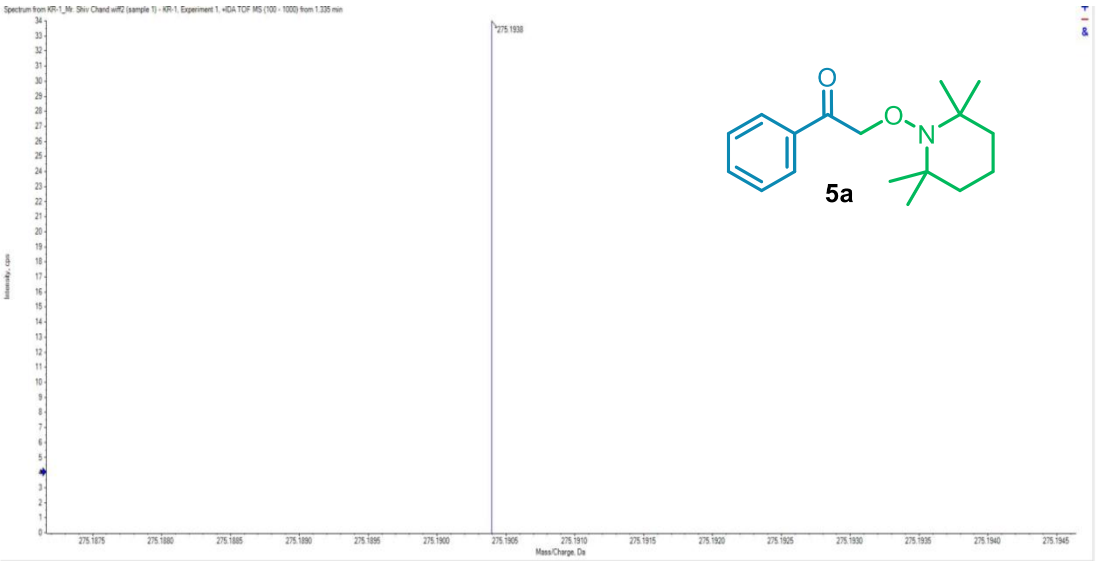


Figure 3.9 HRMS Spectra of **5a**

Figure 3.10 HRMS Spectra of **6a**

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