Chapter 5

A-Chromatography-Free One-Pot, Two-Step Synthesis of 1,2,4-Thiadiazoles from Primary Amides via Thiolation and Oxidative Dimerization under Solvent-Free Conditions: A Greener Approach

5.1 Introduction

Over the past few decades, the formation of S-N bonds has captured the enthusiastic attention of organic chemists due to their crucial role as fundamental building blocks [1]. Among these, 1,2,4-thiadiazole is a highly significant heterocyclic compound in the field of medicinal chemistry and agrochemical research [2]. Its unique molecular structure, consisting of a five-membered ring containing sulfur and nitrogen atoms, offers a robust foundation for designing compounds with specific biological activities [3]. For example, 1,2,4-thiadiazole unit containing compounds I and II have much higher inhibitory activity against aromatase than resveratrol, and compound III, shows neuroprotective properties [4],

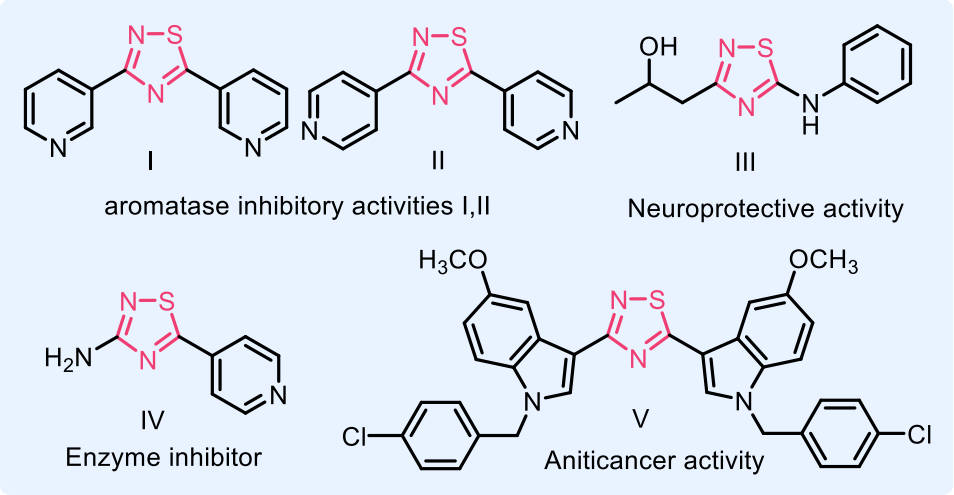


Figure 5.1 Some biologically active 1,2,4-thiadiazoles.

and compound IV may be a potential drug for Alzheimer's disease due to its good β-secretes inhibitory activity [5] 3,5-Bis(indolyl)-1,2,4-thiadiazoles derivatives (e.g., compound V) display in-vitro anticancer activity [6] (**Figure 5.1**).

Given its importance, extensive efforts have been dedicated to developing synthetic methodologies for producing diverse thiadiazoles. Among the various approaches explored, the oxidative dimerization of thioamides stands out as the most promising method. This technique presents a straightforward and expeditious route, exhibiting favorable atom economy synthesizing thiadiazoles.

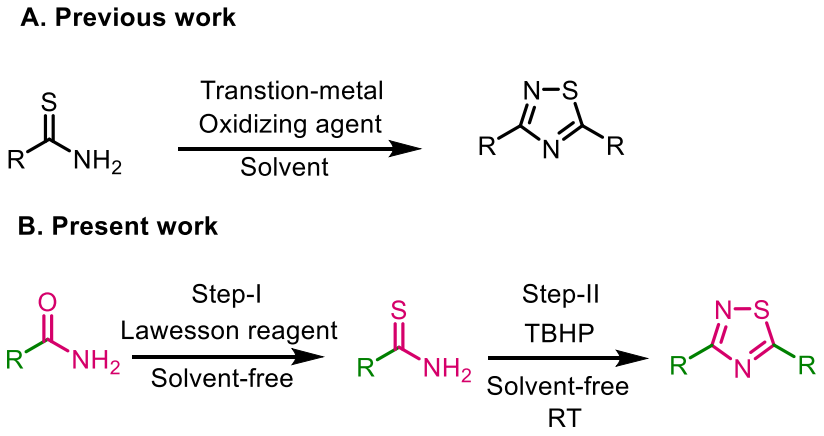
Various metal and metal-free oxidizing reagents, such as ceric ammonium nitrate [7], 2-iodoxybenzoic acid [8], nitrous acid [9], copper-catalyzed [10], N-bromosuccinimide [11], oxone [12], *tert*-butyl Nitrite [13], TCT-DMSO [14], polymer-supported diaryl selenoxide [15], chloranil [16], copper-oxide [17], TCCA [18], p-toluenesulfinic acid [19], Tetra(n-butyl)ammonium peroxydisulfate [20], organotellurium [21], phenyliodine (III) diacetate [22], NH_4I [23], N-benzyl-DABCO tribromide/DMSO [24], Eosin Y/light [25], H_5IO_6 [26], $O_2/I_2/H_2SO_4$ [27], $H_6PV_3Mo_9O_{40}$ [28], and IBA/Tf_2O [29] have been used for dimerization of thioamides. Other substrates, such as aryl nitriles and aryl amidines, have also been reported to synthesize thiadiazoles [30]. In 2018, Pan and co-workers developed an electrochemical method for constructing intermolecular S-N bonds from thioamides without oxidants. However, many of these processes are hampered by excessive reagents,

which result in massive amounts of by-products, harsh reaction conditions, prolonged reaction durations, and time-consuming workup procedures [31]. All the above methods required chromatography purification, which required a large amount of solvents. Developing such a methodology would be highly desirable as it could streamline the synthesis process, reduce the consumption of solvents, lower costs, and make the synthesis more sustainable overall. This pursuit aligns with the principles of green chemistry, aiming to minimize waste and environmental impact while maximizing efficiency and resource utilization.

Amides, characterized by their ready availability, affordability, versatility, stability, biochemical relevance, and natural occurrence [32], are pivotal starting materials in various organic transformations. They can be diversified into different functional groups through processes such as transamidation [33], esterifications [34], and cross-coupling reactions [35]. These attributes make amides particularly advantageous when compared to their thio-analog, thioamides. LR, (Lawesson reagent) a potent, mild, and versatile thionating reagent [36], is commercially accessible and cost-effective. Its primary use involves replacing oxygen with sulfur in amides, resulting in the formation of thioamides, and also in ester functions. TBHP is a well-known oxidant [37] and has received much attention in many oxidation processes to form new C-C, C-N, C-O, C-S, and N-N bonds [38], it is easily available, low cost, and easy to handle [39]. The solvent-free approach aligns with the principles of green chemistry, as they are eco-friendly and reduce pollution to quite an extent. This method enhances laboratory safety by minimizing the potential for solvent-

related accidents and exposure to toxic substances, and it promotes efficiency [43]. Solvent-free reactions are more efficient as they give more selective and are also high-yielding and cost-effective.

The one-pot, two-step synthesis emerges as a potent and efficient strategy in contemporary organic chemistry, facilitating the streamlined assembly of complex molecules [40]. This innovative approach involves executing two separate chemical transformations consecutively within a single reaction vessel, eliminating the necessity for intermediate purification and isolation steps [41]. The advantage of this method lies in its ability to enhance reaction efficiency, reduce waste production, and enhance overall yields. Crucially, it significantly reduces the overall reaction time, underscoring its pivotal role in accelerating synthetic processes [42].



Scheme 5.1 Synthesis of 3,5-disubstituted 1,2,4-thiadiazoles (A) Previous work: From thioamides. (B) Present work: From amides.

In continuation of our work in developing the green methodology to synthesize biologically important small motifs. A one-pot synthetic route would be a beneficial improvement. Herein, we disclose a highly efficient, simple, and environmentally benign, one-pot, tandem method to synthesize 1,2,4-thiadiazoles starting from the corresponding primary amides using Lawesson reagent and *tert*-butyl hydrogen peroxide as an oxidant under metal and solvent-free conditions (**Scheme 5.1**).

As far as our knowledge, this is the first report of a one-pot, two-step synthesis of 1,2,4-thiadiazoles via C-O bond cleavage and new C-S bond formation through a thionation of benzamide. In the second step, thioamide, generated in situ, underwent oxidative dimerization to form 1, 2, and 4-thiadiazoles.

5.2 Results and Discussion

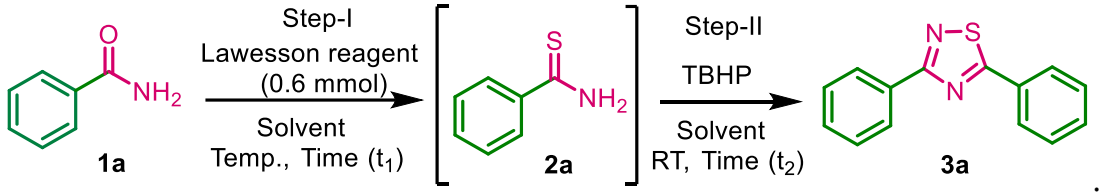
In order to obtain maximum yield of the symmetrical 3,5- diphenyl-1,2,4-thiadiazole **3a** the main efforts were directed towards the best reaction conditions to synthesis **3a**. Initially, we selected benzamide **1a**, Lawesson reagent and TBHP as model substrates to optimize the reaction conditions 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 (**Table 5.1, entry 1**). 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 to prepare 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 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 (**Table 5.1, entry 2**). 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 (**Table 5.1, entries 4-6**). Then, we examined polar protic solvents like ethanol, methanol, and water. Still, very unfortunately, amide **1a** did not convert into the thioamide **2a,** so we failed to proceed to the second step to give product **3a** (**Table 5.1, entries 7-9**).

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 oC under solvent-free conditions for 60 min, which gave intermediate **2a. 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, giving the desired product 3,5-diphenyl-1,2,4-thiadiazoles **3a** in 65% yield (**Table 5.1, entry 10**).

Table 5.1 Optimization of reaction conditions for the synthesis of 3,5-diphenyl- 1,2,4-thiadiazole **3a** from benzamide[a]



S.N	Solvent	TBHP (equv.)	Temp. (°C)	Time (t_1) min	Time (t_2) min	Yield 3a[b] (%)
1[c]	Toluene	1.5	Reflux	60	-	n.r
2	Toluene	1.5	Reflux	60	30	50
3	Benzene	1.5	Reflux	60	30	40
4	THF	1.5	Reflux	60	30	50
5	DCM	1.5	Reflux	60	30	25
6	CH_3CN	1.5	Reflux	60	30	30
7	EtOH	1.5	Reflux	60	-	n.r
8	MeOH	1.5	Reflux	60	-	n.r
9	Water	1.5	Reflux	60	-	n.r
10	Solvent-free	1.5	60	60	3	65
11	Solvent-free	1.5	80	25	3	92
12	Solvent-free	1.5	100	25	3	93
13	Solvent-free	1.0	80	25	3	70
14	Solvent-free	2.0	80	25	3	92
15	Solvent-free	4.0	80	25	3	91

Reaction conditions: Step 1: **1a** (1.0 mmol), Lawesson reagent (0.6 mmol.), and solvent (2 mL) at its reflux temp. Step 2: TBHP (1.5 equiv.) at RT (25-30 ^{O}C). [b] Isolated yield.

[c] Single-step reaction at reflux temp.

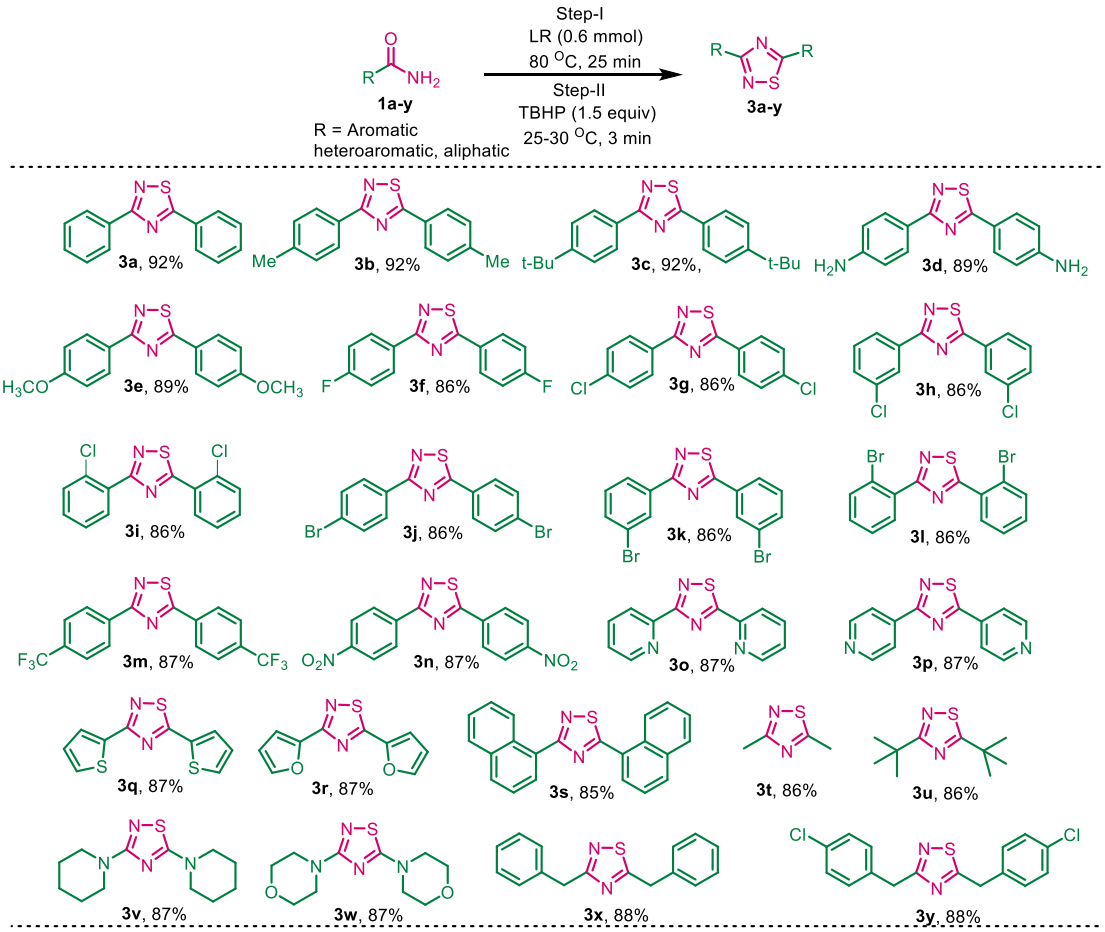
After that, the first step of the reaction was carried out at higher temperatures 80°, and 100 °C. Interestingly, the reaction at 80 °C temperature with LR (25 min) and 1.5 equiv. TBHP, under solvent-free conditions, was driven to completion with the desired product **3a** to a maximum yield of 92% in 3 min (**Table 5.1, entry 11**). 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 product yield (**Table 5.1, entry 12**). Further, 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 (**Table 5.1, entries 13-15).** Thus, the optimized reaction conditions are primary amide **1a** (1.0 mmol), Lawesson reagent (0.6 mmol) at 80 °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 (**Scheme 5.2**, **3a-l**). Furthermore, the strongly electron-withdrawing groups, such as trifluoromethyl and nitro groups these substrates also underwent a reaction smoothly and yielded the desired products **3m** and **3n** in good yields.

Surprisingly, heteroaromatic amides, such as picolinamide, isonicotinamide and thiophene-2-carboxamide, also participated successfully in this reaction, furnishing **3o-3r** in good yields (**Scheme 5.2**). Additionally, 1-naphthyl benzamide was subjected to the same conditions and successfully yielded 3,5-(1,1-dinaphthyl)- 1,2,4-thiadiazoles **3s** 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 **3t-3y** in good yields (**Scheme 5.2**). All the synthesized products were purified without column chromatography by simply recrystallization, saving lots of solvents and our environment from getting polluted. The products (**3a-z**) were characterized by (^{1}H, ^{13}C NMR, and HRMS spectral data) and confirmed by comparing with those reported. The reaction is reasonably clean, rapid, and efficient. Moreover, the simple experimental and isolation procedure makes it a new efficient route for synthesizing diverse 3,5-diaryl-1,2,4-thiadiazoles.

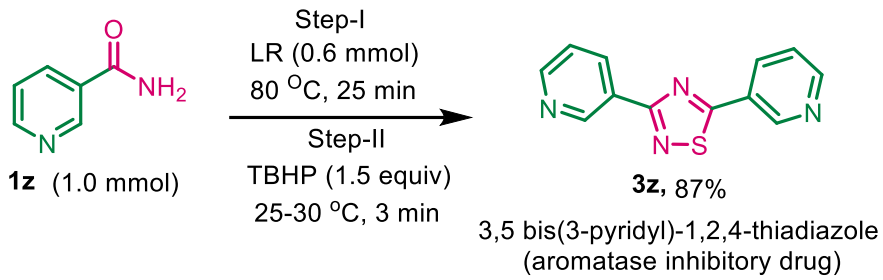
Scheme 5.2 Substrate scope for one-pot two-step synthesis of 1,2,4-thiadiazoles under solvent and catalyst-free (3a-y)[a]



[a]**Reaction conditions**: primary amides (1.0 mmol), Lawesson reagent (0.6 mmol), and TBHP (1.5 equi).

After exploring the scope of various 1, 2, 4-thiadiazoles, we attempted to synthesize 3,5-bis(3-pyridyl)-1,2,4-thiadiazole**,** a promising aromatase inhibitory drug designed to impede the enzymatic conversion of androgen to estrogens within the body, using this developed method. The reaction of *nicotinamide* **1z** (1.0 mmol) with LR (0.6 mmol) and TBHP (1.5 mmol) gave the desired product **3z** in 87% yield (**Scheme 5.3**).

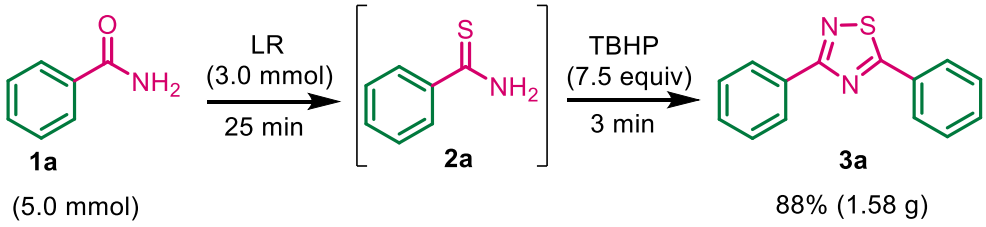
Scheme 5.3. Synthesis of 3,5-bis(3-pyridinyl)-1,2,4-thiadiazole **3z** from nicotinamide in solvent-free condition[a]



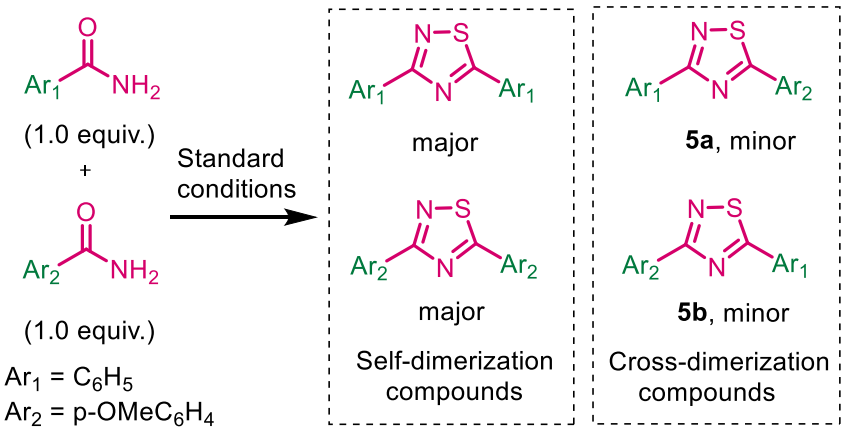
[a]**Reaction conditions:** Nicotinamide **1z** (1.0 mmol), Lawesson reagent (0.6 mmol), and TBHP (1.5 equiv.) in solvent-free condition.

5.3 Gram-Scale Synthesis of 1,2,4-Thiadiazole (3a)

To assess the potential applicability of this methodology in multigram-scale synthesis of 1,2,4-thiadiazole **3a.** The experiment was conducted using benzamide **1a** (5.0 mmol), LR (3.0 mmol), and TBHP (7.5 mmol) under standard conditions. The product **3a** was obtained in 88% yield (**Scheme 5.4**). The experimental work showed a robust and acceptable gram-scale synthesis of 1,2,4-thiadiazole.



Scheme 5.4 Synthesis of **3a** product on gram-scale.



Scheme 5.5. Cross-dimerization reaction reaction.

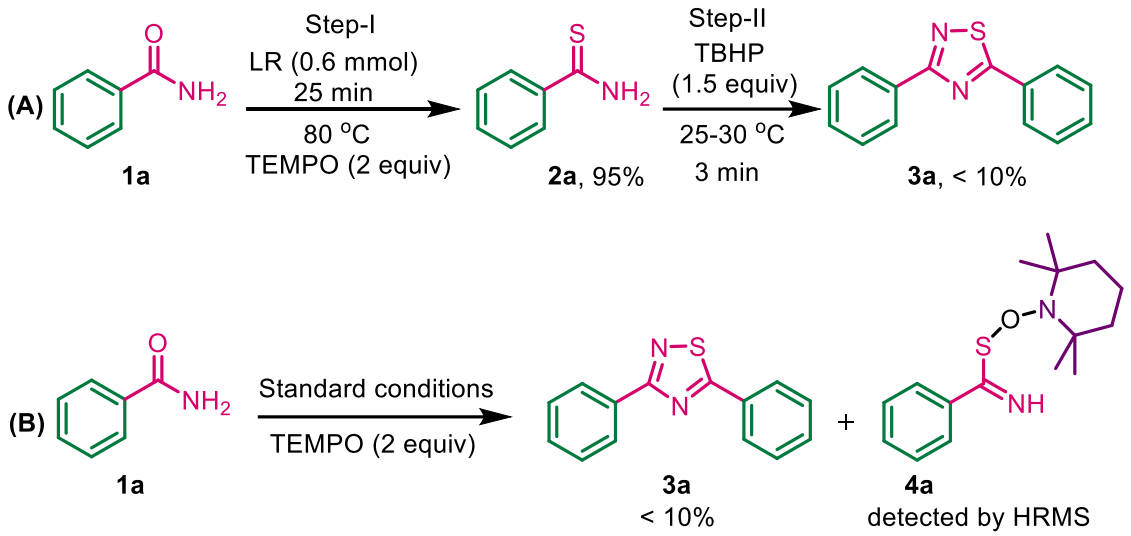
Next, we investigated the cross-dimerization reaction using benzamide and *p*-methoxybenzamide under standard conditions (**Scheme 4.5**). Unfortunately, corresponding self-dimerization compounds were obtained as the major products (35% yields), and cross-dimerization compounds were obtained as minor products **5a** and **5b**.

5.4 Optimized experiments

5.1.1 Mechanistic Study; Radical Trapping Experiment by TEMPO

To investigate the plausible reaction mechanism, a control experiment was carried out among benzamide, Lawesson reagent, and radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-yl) oxy) (2 equiv.) (**Scheme 5.6, A**), gave 95% yield of **2a**, this indicates the thiolation of amide did not quench by TEMPO, so the first step is not a radical path. In the second step, TBHP was added to the above reaction mixture at room temperature. The dimerization process was inhibited by TEMPO, which is already present in the reaction mixture, and less than 10% of the desired product **3a** was obtained, and

thiobenzamide-TBHP adduct was isolated (**Scheme 5.6 B**), indicating that the formation of 1,2,4-thiadiazole involved a radical mechanistic pathway in the second step.

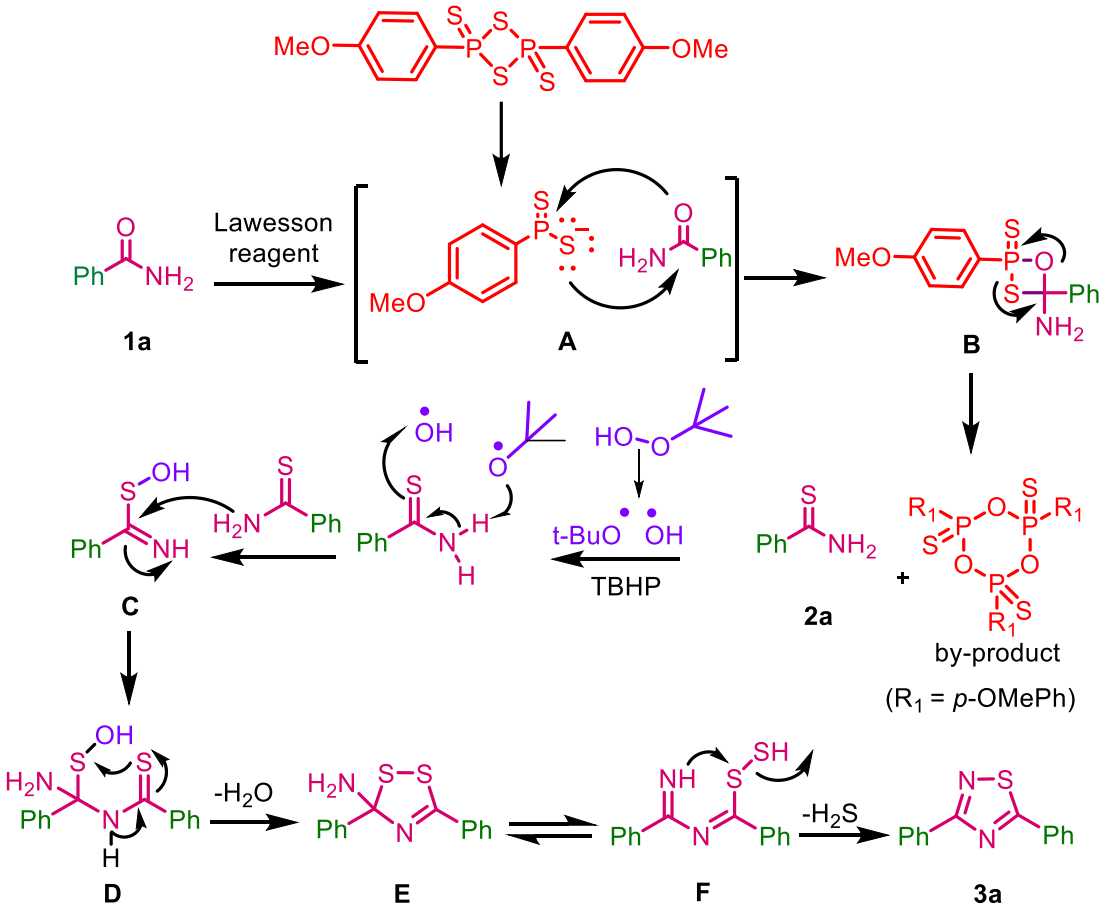


Scheme 5.6 Control experiment with TEMPO.

5.5 Proposed Mechanism

A plausible reaction mechanism for one-pot, two-step synthesis of 1,2,4-thiadiazoles from primary amides with Lawesson reagent and *tert*-butyl hydrogen peroxide is depicted in (**Scheme 5.7**). In the first step the reactive species dithiophosphine ylide **A** of Lawesson reagent reacts with benzamide **1a** and gives thioxaphosphenate intermediate **B**; it undergoes cycloreversion to give thiobenzamide **2a** along with the by-product 2,4,6-tris(4-methoxyphenyl)-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trisulfide, which was confirmed by melting point and HRMS data (**Figure 5.12**). In the second step, TBHP undergoes radical dissociation to form *tert*-butoxy and hydroxyl radicals, which may react with

thiobenzamide to form intermediate **C**. This intermediate may undergo dimerization by eliminating water (H_2O) through intermediate **D** to form intermediate **E**. This may be in equilibrium with intermediate **F,** and it might eliminate hydrogen sulfide (H_2S) to give the desired product **3a**.



Scheme 5.7 Plausible reaction mechanism for one-pot two-step synthesis of 1,2,4-thiadiazoles.

5.6 Conclusion

In conclusion, we have demonstrated an efficient and greener protocol for synthesizing 1,2,4-thiadiazoles using primary amides, Lawesson reagent, and TBHP under solvent-free conditions. This is the first report of a one-pot, two-step synthesis of 1,2,4-thiadiazoles via C-O bond cleavage and new C-S bond formation through a thionating reagent (Lawesson reagent) and TBHP. The current protocol found broad substrate scope, excellent functional group tolerance, metal-free conditions, quick conversion, and excellent yields are essential features of this methodology. Since there is no workup and purification of the thioamide intermediate, it saves lots of solvent and time. In addition to its efficiency and simplicity, this study provides a valuable alternative to the prevailing methods for synthesizing biologically active 3,5-diaryl/alkyl-1,2,4-thiadiazoles.

5.7 Experimental Procedure

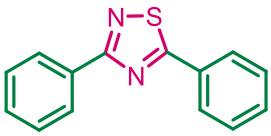
5.7.1 General Procedure for the Synthesis of 3,5-Disubstituted-1,2,4-Thiadiazoles.

An oven-dried round bottom flask (25 ml) equipped with a stir bar was charged with primary amide (1.0 mmol) and Lawesson reagent (0.6 mmol). The reaction mixture was heated at 80 °C, and the progress of the reaction was monitored by TLC. After completion of the reaction (25 min) it was cooled to room temperature, and TBHP (1.5 equivalent) was added to the mixture and stirred at room temperature further; the progress of the reaction was monitored by TLC. After completion of the reaction, the solid mixture was extracted with ethyl acetate, washed with water and undissolved byproduct **A** was isolated by

filtration. Byproduct **A** was recrystallized from benzene and confirmed by melting point and mass spectra. The organic layer was dried over Na_2SO_3, and the solvent was removed under reduced pressure. The product was purified by recrystallization with ethanol to obtain the desired 1,2,4-thiadiazoles. All the products were characterized by ^1H, ^{13}C-NMR, and HRMS.

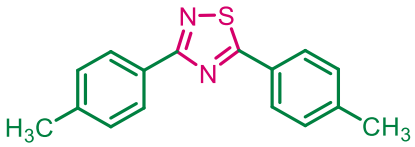
5.8 Analytical data of products; ^1H, ^{13}C, ^{19}F & HRMS spectral data

3,5-diaryl-1,2,4-thiadiazoles (3a)



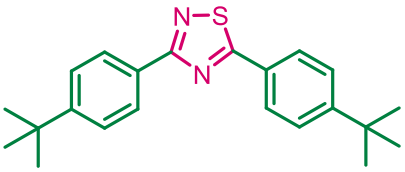
Yield: 92%; White solid; m.p. 91 ºC; **^1H NMR** (500 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 7.9, 1.7 Hz, 2H), 8.09 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.59-7.49 (m, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 188.2, 173.8, 132.9, 131.9, 130.7, 130.4, 129.3, 128.7, 4 128.4, 127.5 ppm. HRMS (ESI) calculated for $C_{14}H_{10}N_2S$ [$M+H^+$]: 239.0643, found 239.0668.

3,5-dip-tolyl-1,2,4-thiadiazole (3b)



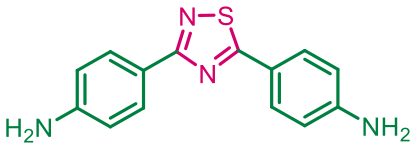
Yield: 92%; White solid; m.p. 134-136 ºC; **^1H NMR** (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.1 Hz, 2H), 7.93 (d, *J* = 8.1 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 4H), 2.44 (d, *J* = 5.0 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 188.1, 173.9, 142.6, 140.6, 130.5, 130.0, 129.5, 128.4, 128.3, 127.6, 21.7, 21.6 ppm. HRMS: (ESI) calculated for $C_{16}H_{14}N_2S$[$M+H^+$]: 267.0956, found 267.0953.

3,5-bis(4-tert-butylphenyl)-1,2,4-thiadiazole (3c)



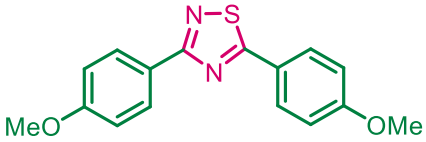
Yield 92%; White solid; m.p. 91 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 8.3 Hz, 2H), 7.57-7.54 (d, *J* = 8.4 Hz, 4H), 1.40 (s, 17H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 188.0, 173.9, 155.7, 153.7, 130.5, 128.3, 128.3, 127.4, 126.3, 125.8, 35.2, 35.0, 31.4, 31.2 ppm. HRMS (ESI) calculated for $C_{22}H_{26}N_2S$ [M+H$^+$]: 351.1895, found 351.1904.

3,5-bis(4-aminophenyl)-1,2,4-thiadiazole (3d)



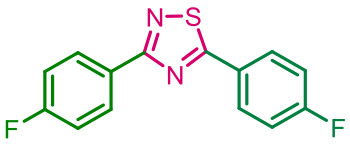
Yield 89%; Orange-yellow solid; m.p. 208-209 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.7 Hz, 1H), 7.87-7.82 (d, *J* = 8.7 Hz, 1H), 7.45-7.42 (d, *J* = 8.7 Hz, 4H), 4.17 (br s, *J* = 8.7 Hz, 4H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.4, 133.8, 129.8, 129.3, 129.2, 120.0, 114.7, 114.7, 114.4, 113.7, 100.3 ppm. HRMS (ESI) calculated for $C_{14}H_{12}N_4S$ [M+H$^+$]: 269.0781, found269.0790.

3,5-bis(4-methoxyphenyl)-1,2,4-thiadiazole (3e)



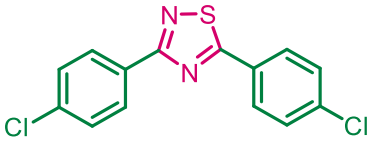
Yield: 89%; White solid; m.p. 139-141 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 4H), 3.89 (s, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 187.3, 173.4, 162.5, 161.3, 129.9, 129.2, 126.0, 123.7, 114.6, 113.9, 55.5, 55.3 ppm. HRMS (ESI) calculated for $C_{16}H_{14}N_2O_2S$ [M+H$^+$]: 299.0854, found 299.0823.

3,5-bis(4-fluorophenyl)-1,2,4-thiadiazole (3f)



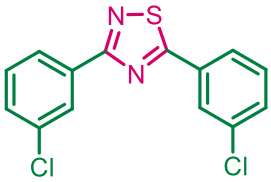
Yield 85%; White solid; m.p. 184-187 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 8.9, 5.5 Hz, 2H), 8.04 (dd, *J* = 8.9, 5.2 Hz, 2H), 7.23-7.16 (m, 4H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 187.1, 172.9, 166.0 (d, *J* = 253.2 Hz), 165.3 (d, *J* = 250.1 Hz), 130.6 (d, *J* = 8.2 Hz), 129.8 (d, *J* = 8.8 Hz), 129.2 (d, *J* = 3.7 Hz), 127.1 (d, *J* = 2.5 Hz), 116.7 (d, *J* = 22.6 Hz), 115.9 (d, *J* = 21.4 Hz) ppm. HRMS: (ESI) calculated for $C_{14}H_8F_2N_2S$ [M+H$^+$]: 275.0455, found 275.0455.

3,5-bis(4-chlorophenyl)-1,2,4-thiadiazole (3g)



Yield 86%; White solid; m.p. 161-163 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.6 Hz, 2H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.59-7.49 (dd, *J* = 16.4, 8.6 Hz, 4H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 187.6, 172.7, 138.3, 136.8, 131.3, 129.8, 129.9, 128.2, 129.1, 128.8 ppm. HRMS: (ESI) calculated for $C_{14}H_8Cl_2N_2S$ [M+H$^+$]: 306.9863, found 306.9865.

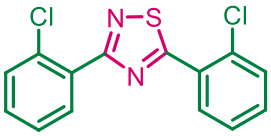
3,5-bis(3-chlorophenyl)-1,2,4-thiadiazole (3h)



Yield 86%; White solid, m.p. 125-127 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.30 (d, *J* = 1.8 Hz, 1H), 8.16 (dd, *J* = 7.0 Hz, 1H), 8.05 (d, *J* = 1.9 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.51-7.50 (m, 4H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 186.9, 172.9, 134.2, 134.1, 132.2, 131.1,

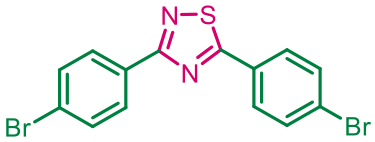
131.0, 130.2, 130.0, 129.9, 128.1,127.2, 126.4 ppm. HRMS (ESI) calculated for [M+H$^+$]: 306.9795 $C_{14}H_8Cl_2N_2S$ found 306.9790.

3,5-bis(2-chlorophenyl)-1,2,4-thiadiazole (3i)



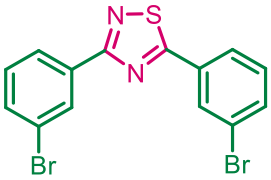
Yield 86%; White solid, m.p. 91-93 ^oC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.67 (d, *J* = 1.8 Hz, 1H), 8.08 (dd, *J* = 7.0 Hz, 1H), 7.99-7.55 (m, 2H), 7.48-7.41 (m, 4H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 184.5, 170.7, 134.1, 134.0, 132.2, 132.2, 131.7, 131.5, 130.9, 127.9, 127.6 127.4, 123.5, 122.2 ppm. HRMS (ESI) calculated for [M+H$^+$]: 306.9795 $C_{14}H_8Cl_2N_2S$ found 306.9791.

3,5-bis(4-bromophenyl)-1,2,4-thiadiazole (3j)



Yield 86%; White solid; m.p. 150-151 ^oC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.35-8.33 (d, *J* = 7.8 Hz, 1H), 8.01-8.00 (d, *J* = 7.6 Hz, 1H), 7.54-7.49 (m, 4H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 187.9, 172.9, 136.6, 131.9, 129.7, 129.6, 129.0, 128.9, 128.8, 128.7 ppm. HRMS (ESI) calculated for 394.8775, [M+H$^+$]: $C_{14}H_8Br_2N_2S$ found 394.8780.

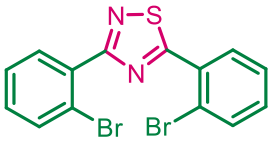
3,5-bis(3-bromophenyl)-1,2,4-thiadiazole (3k)



Yield 86%; White solid; m.p. 113-114 ^oC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.25 (d, *J* = 7.8 Hz, 1H), 8.99 (d, *J* = 7.6 Hz, 1H), 8.53 (d, *J* = 7.5 Hz, 1H), 8.09 (m, 1H), 7.99 (m, 2H), 7.66-7.65 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 184.5, 170.6, 134.1, 134.0, 133.2,

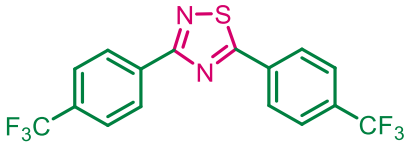
132.2, 131.7, 131.5, 1309, 127.9, 127.6, 127.4, 123.4, 122.2 ppm. HRMS (ESI) calculated for 394.8775, $[M+H^+]$: $C_{14}H_8Br_2N_2S$ found 394.8771.

3,5-bis(2-bromophenyl)-1,2,4-thiadiazole (3l)



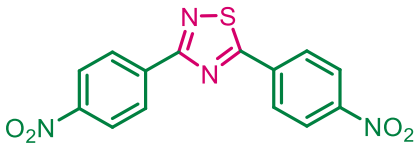
Yield 86%; White solid; m.p. 97 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 7.5 Hz, 2H), 7.55-7.52 (m, 2H), 7.37-7.34 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 184.6, 170.8, 134.1, 134.0, 134.0, 132.2, 132.2, 131.7, 1315, 130.9, 127.9, 127.4, 123.4, 122.2 ppm. HRMS (ESI) calculated for 394.8858, $[M+H^+]$: $C_{14}H_8Br_2N_2S$ found 394.8853.

3,5-bis(trifluoromethyl)phenyl-1,2,4-thiadiazole (3m)



Yield 85%; White solid; m.p. 80 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.1 Hz, 2H), 8.21 (d, *J* = 8.1 Hz, 2H), 7.84-7.79 (dd, *J* = 17.5, 8.1 Hz, 4H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 186.9, 172.7, 135.6, 133.8(q, *J* = 32.7 Hz), 128.6 (q, *J* = 32.4 Hz), 128.6, 127.9, 127.8, 126.4 (q, *J* = 3.7 Hz), 125.7 (q, *J* = 3.7 Hz), 124.6 (q, *J* = 270.7 Hz), 122.8 (q, *J* = 270.9 Hz) ppm. HRMS: (ESI) calculated for $C_{16}H_8F_6N_2S$ $[M+H^+]$: 375.0391, found 375.0412.

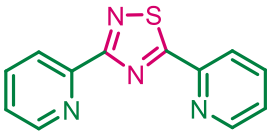
3,5-bis(4-nitrophenyl)-1,2,4-thiadiazole (3n)



Yield 85%; Pale yellow solid; m.p. 200-202 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.2 Hz, 2H), 8.45-8.37 (m, 4H), 8.26-8.24 (d, *J* = 8.2 Hz, 2H) ppm. **^{13}C NMR** (126 MHz,

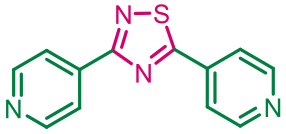
$CDCl_3$) δ 186.8, 172.4, 149.8, 148.9, 137.9, 135.9, 129.5, 128.6, 124.9, 124.3 ppm. HRMS (ESI) calculated for $C_{14}H_8N_4O_4S$ [M+H$^+$]: 329.0270, found 329.0274.

3,5-bis(2-pyridinyl)-1,2,4-thiadiazole (3o)



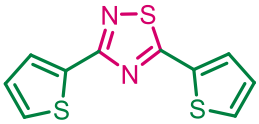
Yield 83%; Yellow solid; m.p. 133 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 4.1 Hz, 2H), 7.69 (d, *J* = 1.7 Hz, 2H), 7.57-7.55 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 185.6, 166.3, 151.3, 149.7, 144.1, 143.2, 140.5, 140.1 128.4, 126.7, 124.2, 123.7, 96.2 ppm. HRMS: (ESI) calculated for $C_{12}H_8N_4S$ [M+H$^+$]: 241.0548, found 241.0556.

3,5-bis(4-pyridinyl)-1,2,4-thiadiazole (3p)



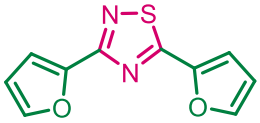
Yield 83%; White solid; m.p. 195-196 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.93-8.88 (m, 4H), 8.35-8.33 (m, 2H), 8.02-8.00 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 186.7, 172.1, 151.3, 150.3, 139.9, 136.8, 122.2, 120.9 ppm. HRMS: (ESI) calculated for $C_{12}H_8N_4S$ [M+H$^+$]: 241.0470, found 241.0475.

3,5-di-thiophen-2-yl-[1,2,4]thiadiazole (3q)



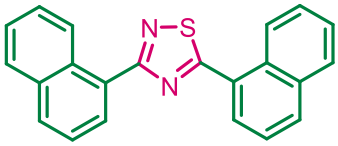
Yield 84%; White solid; m.p. 121 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.25 (d, *J* = 8.6 Hz, 1H), 8.99 (d, *J* = 8.5 Hz, 1H), 8.53 (dd, *J* = 7.2, 0.9 Hz, 1H), 8.11-7.98 (m, Hz, 5H), 7.71-7.59 (m, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 180.6, 168.4, 136.1, 133.1, 130.5, 129.9, 129.3, 129.8, 128.5, 127.9 ppm. HRMS: (ESI) calculated for$C_{10}H_6N_2S_3$ [M+H$^+$]: 250.9699, found 250.09710.

3,5-di-furan-2-yl-[1,2,4]thiadiazole (3r)



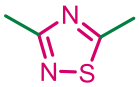
Yield 84%; White solid; m.p. 61-62 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.6 Hz, 1H), 7.23-7.22 (d, *J* = 8.5 Hz, 1H), 6.52 (dd, *J* = 7.2, 0.9 Hz, 1H), 6.35-6.30 (m, Hz, 1H), 6.28 (m, 1H), 6.22-6.20 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.1, 165.0, 148.0, 146.6, 145.9, 144.6, 112.9, 111.8 ppm. HRMS: (ESI) calculated for $C_{10}H_6N_2S_3$ [M+H$^+$]: 219.0150, found 219.0154.

3,5-di-(naphthalalen-1-yl)-1,2,4-thiadiazole (3s)



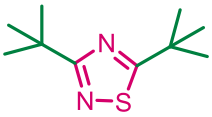
Yield 85%; White solid; m.p. 121 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.25 (d, *J* = 8.6 Hz, 1H), 8.99 (d, *J* = 8.5 Hz, 1H), 8.53 (dd, *J* = 7.2, 0.9 Hz, 1H), 8.11-7.98 (m, Hz, 5H), 7.71-7.59 (m, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 186.9, 173.9, 134.2, 134.1, 132.2, 131.2, 131.0, 130.2, 129.9, 129.3, 128.7, 128.6, 128.0, 127.8, 127.3, 126.8, 126.4, 126.1, 125.4, 125.2, 125.2 ppm. HRMS: (ESI) calculated for$C_{22}H_{14}N_2S$ [M+H$^+$]: 339.0956, found 339.0965.

3,5-dimethyl-1,2,4-thiadiazole (3t)



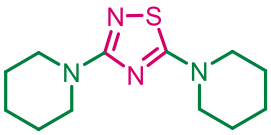
Yield 86%; Yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.47(s, 3H), 2.60 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 189.2, 174.2, 18.5, 16.6 ppm. HRMS: (ESI) calculated for $C_4H_6N_2S$ [M+H$^+$]: 115.0258, found 115.0260.

3,5-di-tert-butyl-1,2,4-thiadiazole (3u)



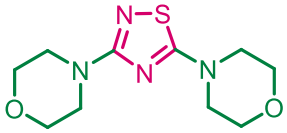
Yield 86%; Yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.57(m, 9H), 1.48 (m, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 188.0, 173.9, 37.8, 35.2, 31.4, 28.2 ppm. HRMS: (ESI) calculated for $C_4H_6N_2S$ [M+H$^+$]: 199.1191, found 199.1195.

3,5-di-piperidine-1-yl-[1,2,4]thiadiazole (3v)



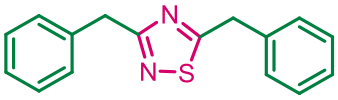
Yield 87%; Yellow solid; m.p. 121 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.87 (d, *J* = 5.2 Hz, 4H), 3.65 (d, *J* = 5.1 Hz, 4H), 1.51 (m, 6H), 1.28 (m, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 184.0, 168.4, 48.2, 46.8, 25.9, 25.3, 24.5 24.0 ppm. HRMS: (ESI) calculated for $C_{12}H_8N_4S$ [M+H$^+$]: 253.1409, found 253.1404.

3,5-di-morpholine-4-yl-1,2,4-thiadiazole (3w)



Yield 87%; Yellow solid; m.p. 133 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.79-3.76 (m, 8H), 3.63-3.60 (m, 2H), 3.54-3.50 (m, 4H), 3.49-3.32 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 184.0, 168.4, 66.2, 66.0, 48.2, 46.8 ppm. HRMS: (ESI) calculated for $C_{12}H_8N_4S$ [M+H$^+$]: 281.0994, found 281.0998.

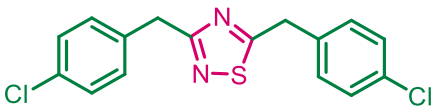
3,5-di-benzyl-1,2,4-thiadiazole (3x)



Yield 88%; Yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.50 (m, 2H), 7.68-7.67 (m, 1H), 7.56-7.54 (m, 2H), 7.41 (m, 2H), 7.36 (m, 2H), 7.28 (m, 1H1), 4.47 (s, 4H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 187.3, 176.9, 136.9, 134.8, 134.3, 131.3, 129.2, 128.9, 128.8, 127.1,

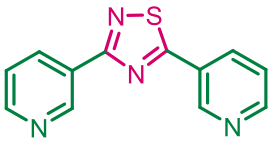
39.6, 37.2 ppm. HRMS: (ESI) calculated for $C_{16}H_{14}N_2S$ [M+H$^+$]: 267.0956, found 267.0957.

3,5-bis(4-chloro-benzyl)-[1,2,4]thiadiazole (3y)



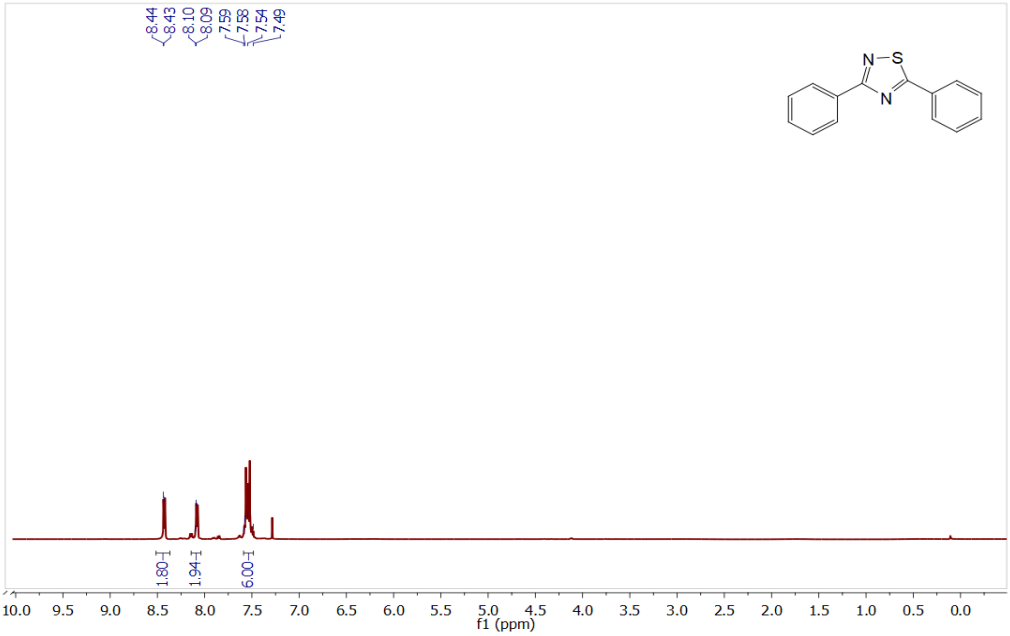
Yield 88%; Yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70-7.67 (m, 2H), 7.55-7.53 (m, 2H), 7.41-7.40 (m, 2H), 7.36-7.35 (m, 2H), 4.47 (s, 4H), ppm.**^{13}C NMR** (126 MHz, $CDCl_3$) δ 187.2, 181.8, 176.5, 141.8, 135.2, 133.2, 132.7, 132.5, 130.6, 129.4, 129.0, 38.9, 29.8 ppm. HRMS: (ESI) calculated for $C_{16}H_{14}N_2S$ [M+H$^+$]: 335.0098, found 335.0092.

3,5-bis(3-pyridinyl)-1,2,4-thiadiazole (3z)



Yield 85%; White Solid; m.p. 132-135 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.63 (d, 1H), 9.29 (d, 1H), 9.05 (d, 1H), 8.83 (m, 1H), 8.76-8.73 (m, 1H), 8.68-8.67 (m, 1H), 7.55-7.52 (m, 1H), 7.50-7.47 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 185.6, 171.6, 152.8, 151.3, 149.7, 148.5, 135.6, 134.6, 128.4, 126.7, 124.2, 123.7 ppm. HRMS: (ESI) calculated for$C_{12}H_8N_4S$ [M+H$^+$]: 241.0548, found 241.0556.

5.9 Spectral Data of Few Products



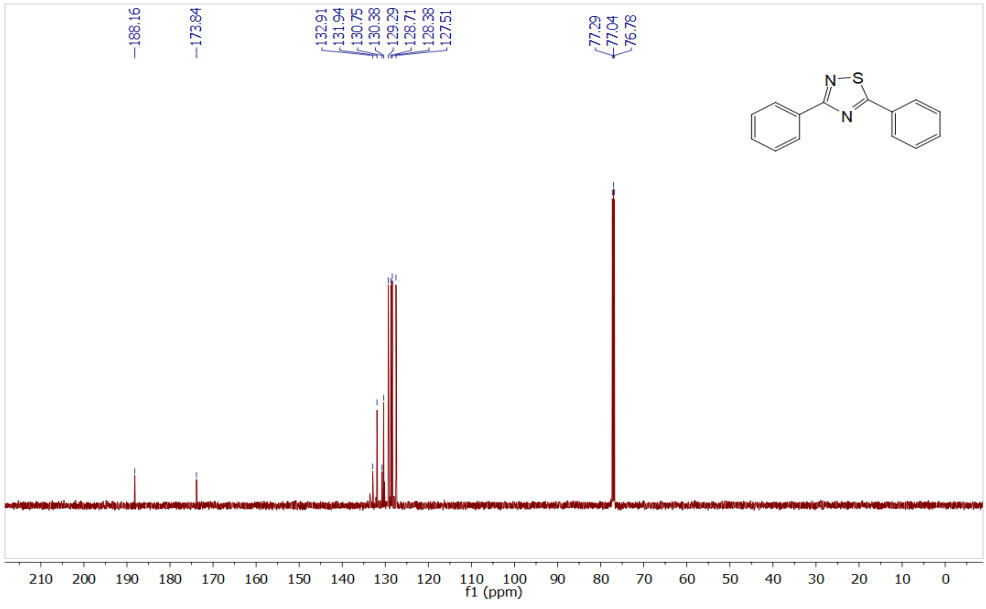


Figure 5.2 ^{1}H & ^{13}C NMR of product **3a**

HRMS Spectra 3a

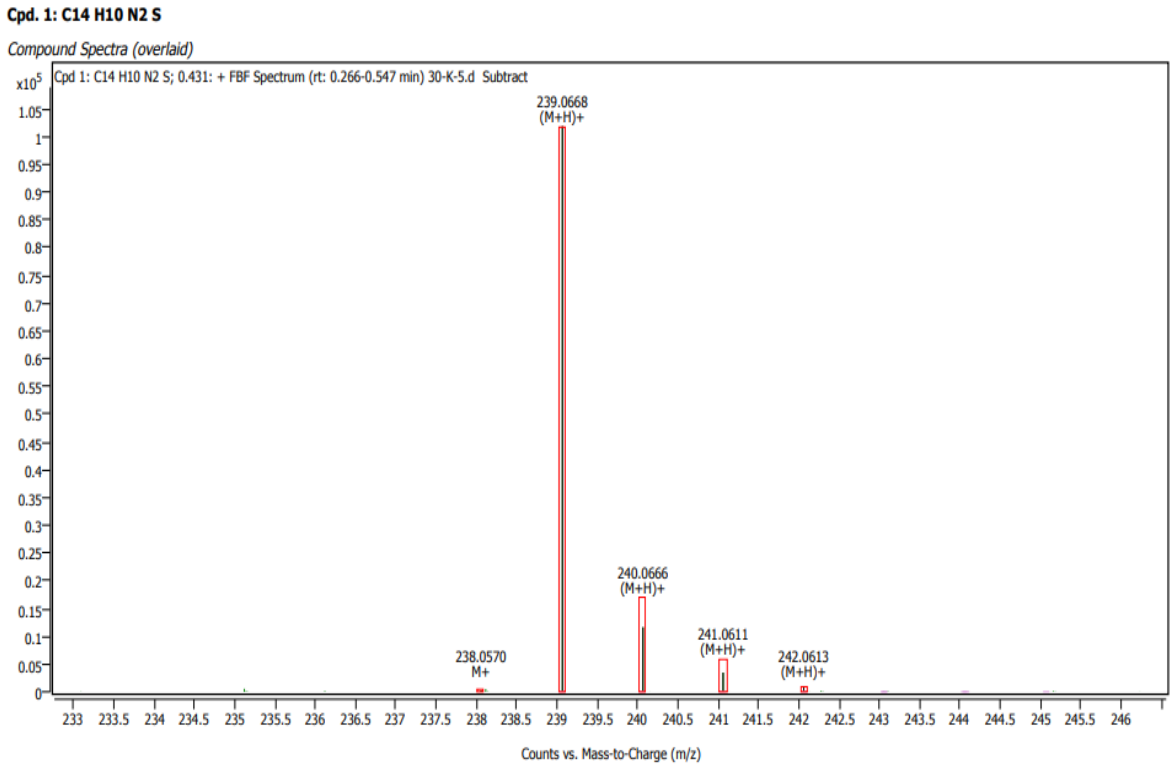
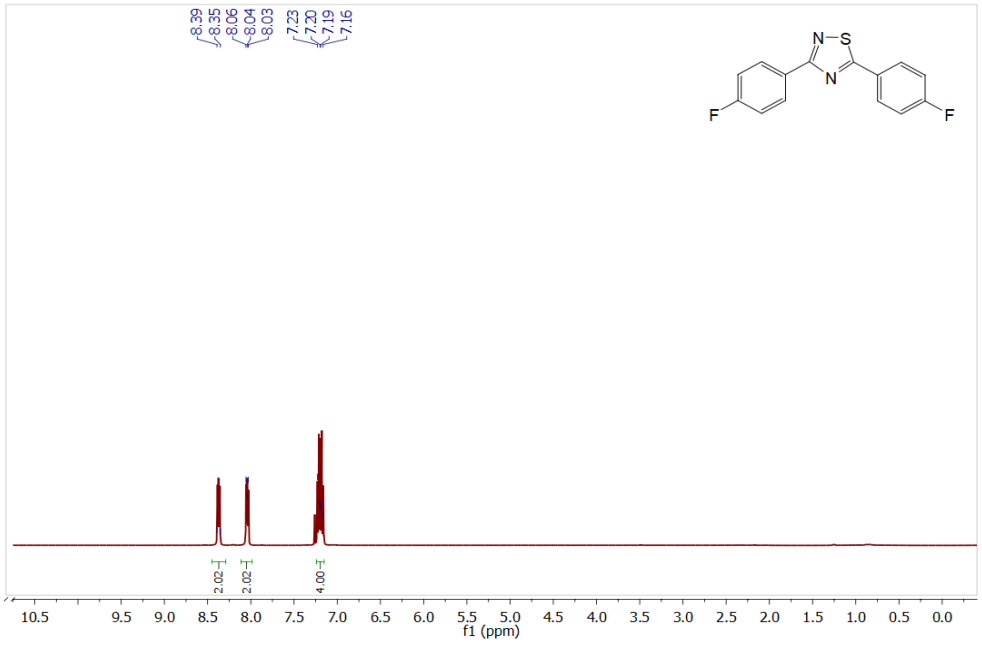


Figure 5.3 HRMS Spectra of **3a**


8.39
8.35
8.06
8.04
8.03
7.23
7.20
7.19
7.16
N
S
N
F
F
2.02
2.02
4.00
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

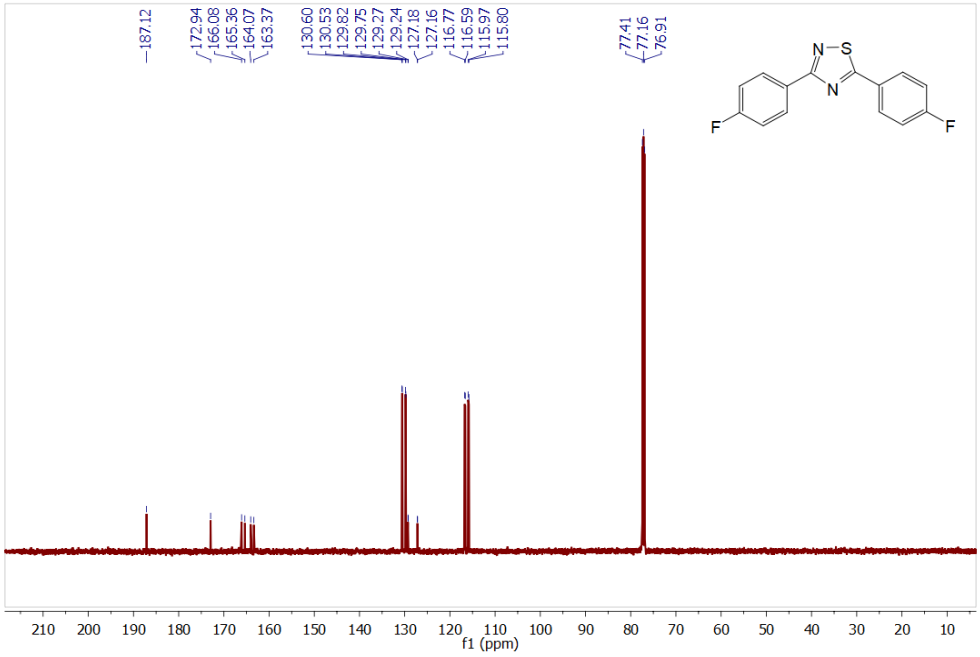


Figure 5.4 ^{1}H & ^{13}C NMR of product **3f**

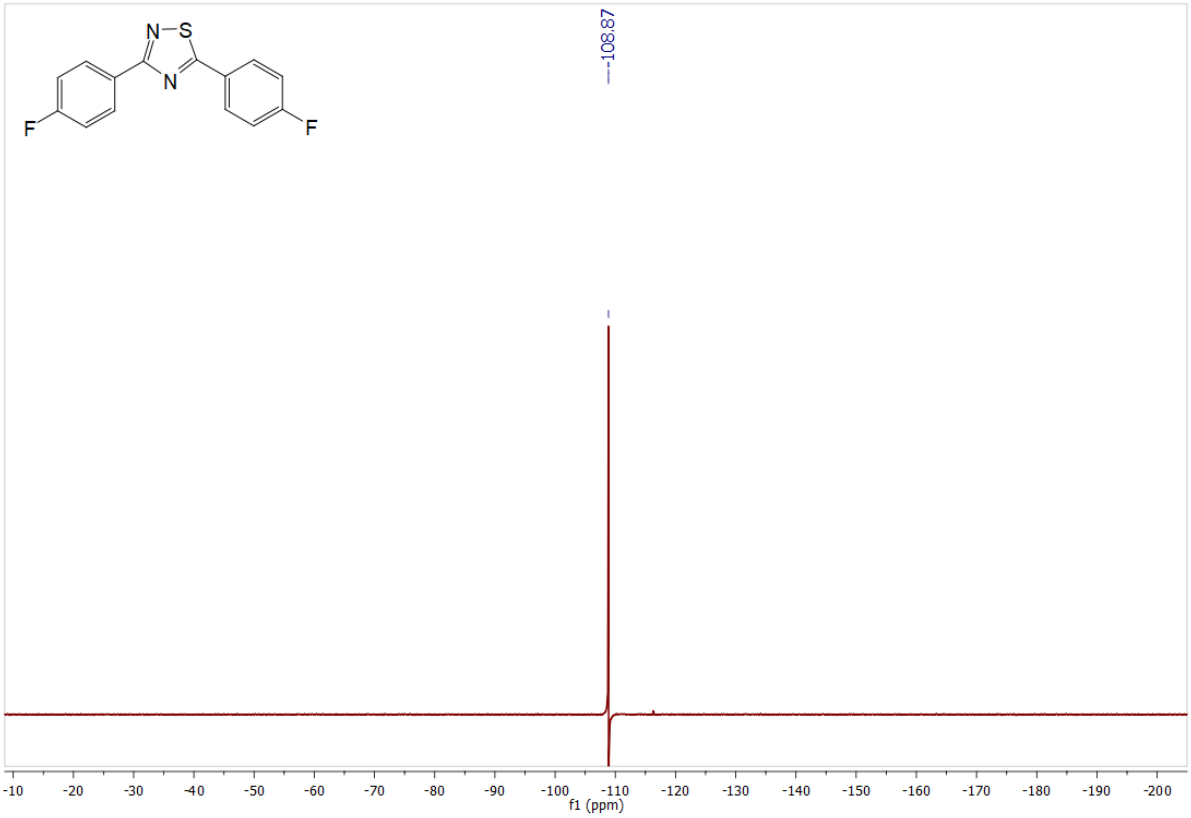


Figure 5.5 ^{19}F NMR Spectra for **3f**

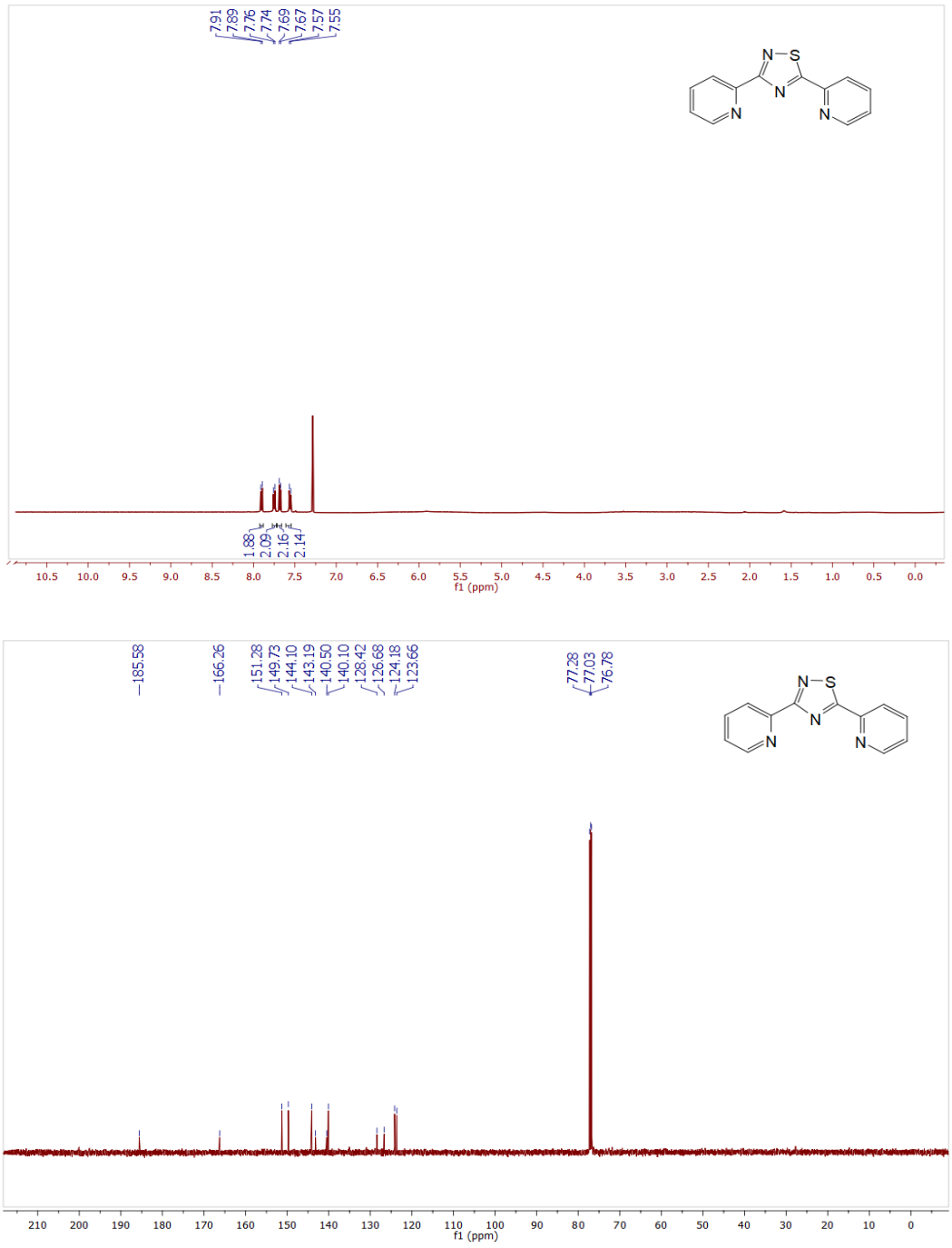


Figure 5.6 ^{1}H & ^{13}C NMR of product **3o**

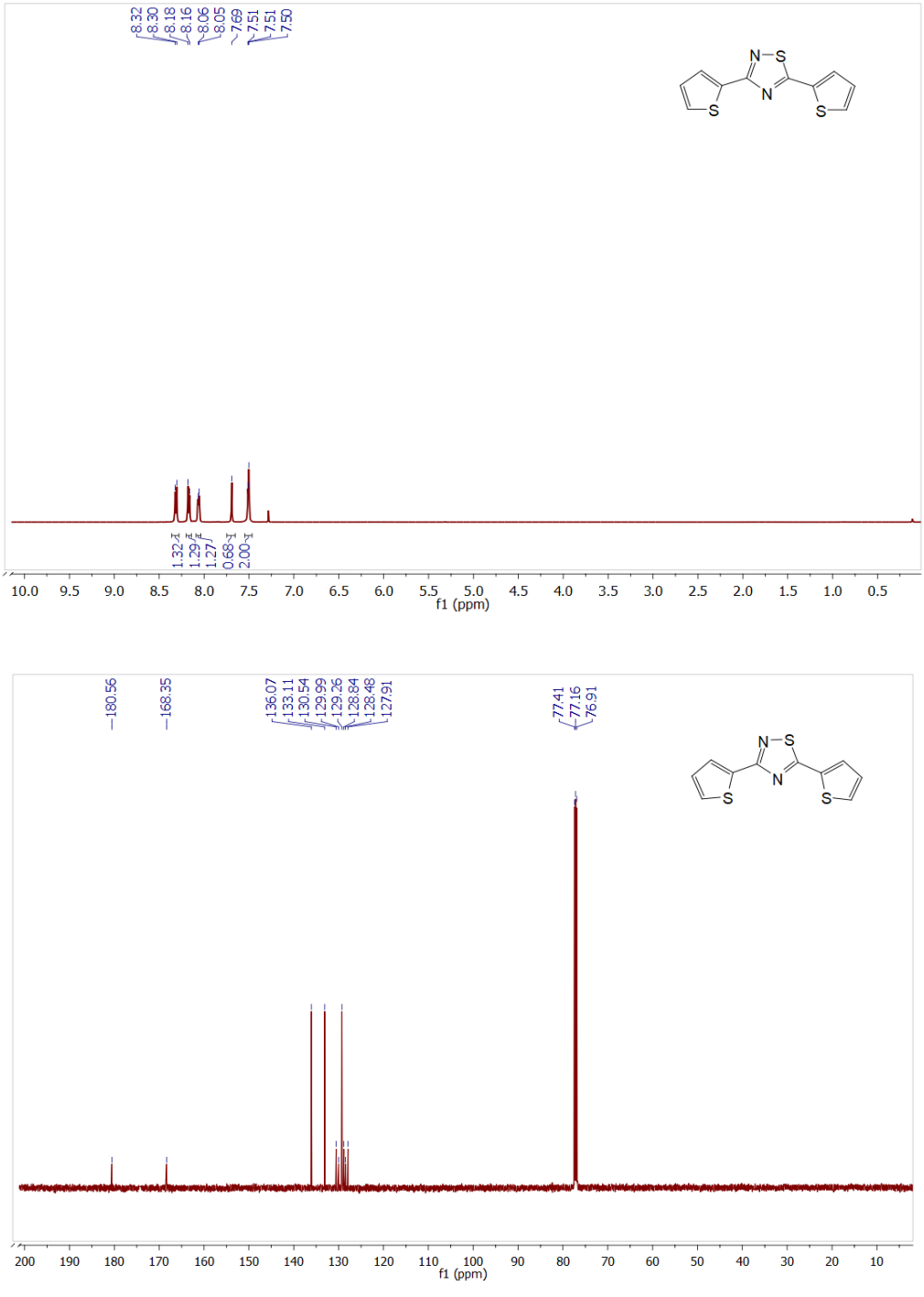


Figure 5.7 ^{1}H & ^{13}C NMR of product **3q**

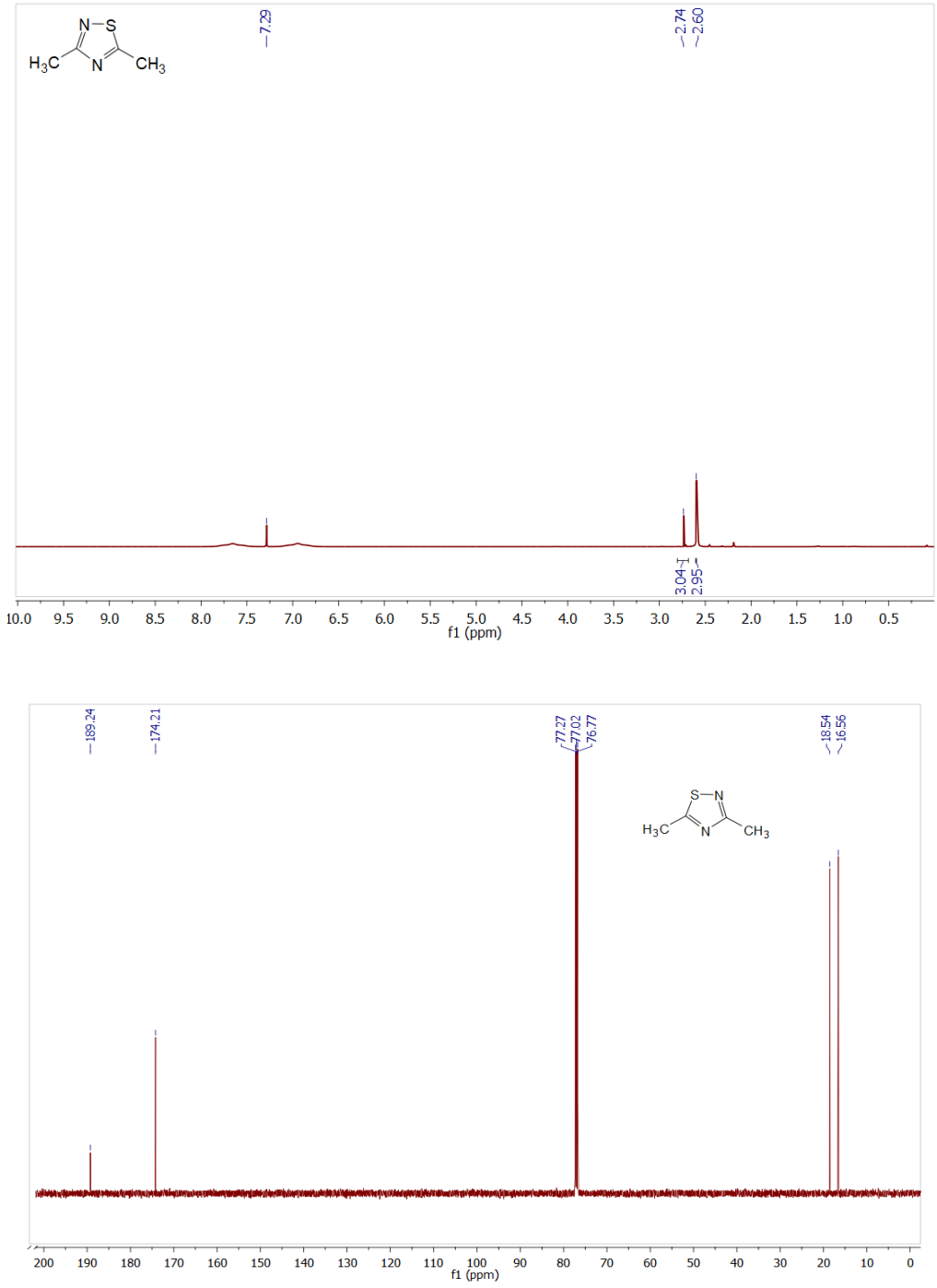


Figure 5.8 ^{1}H & ^{13}C NMR of product **3t**

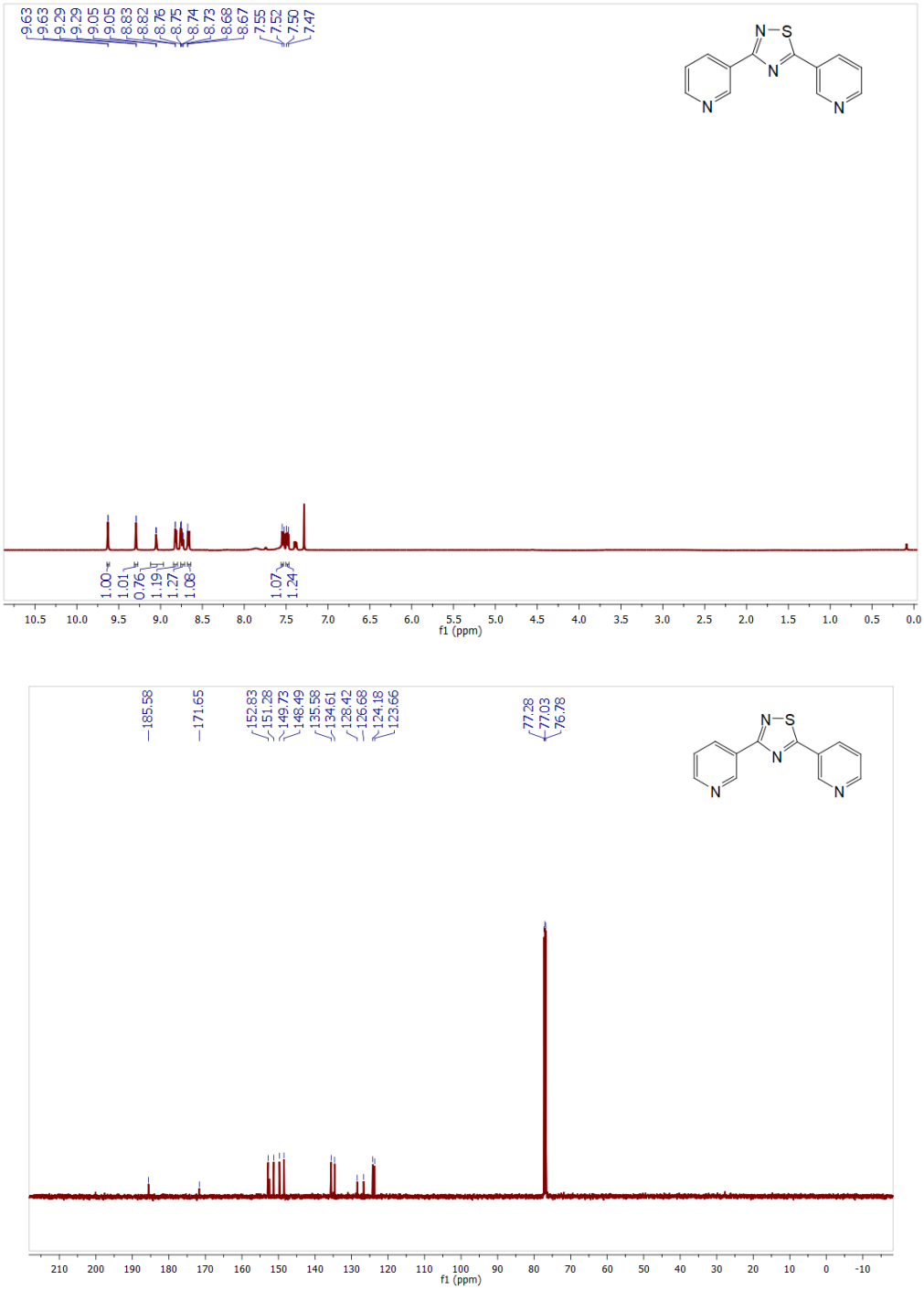


Figure 5.9 ^{1}H & ^{13}C NMR of product **3z**

^{1}H & ^{13}C NMR of 5a & 5b in $CDCl_3$

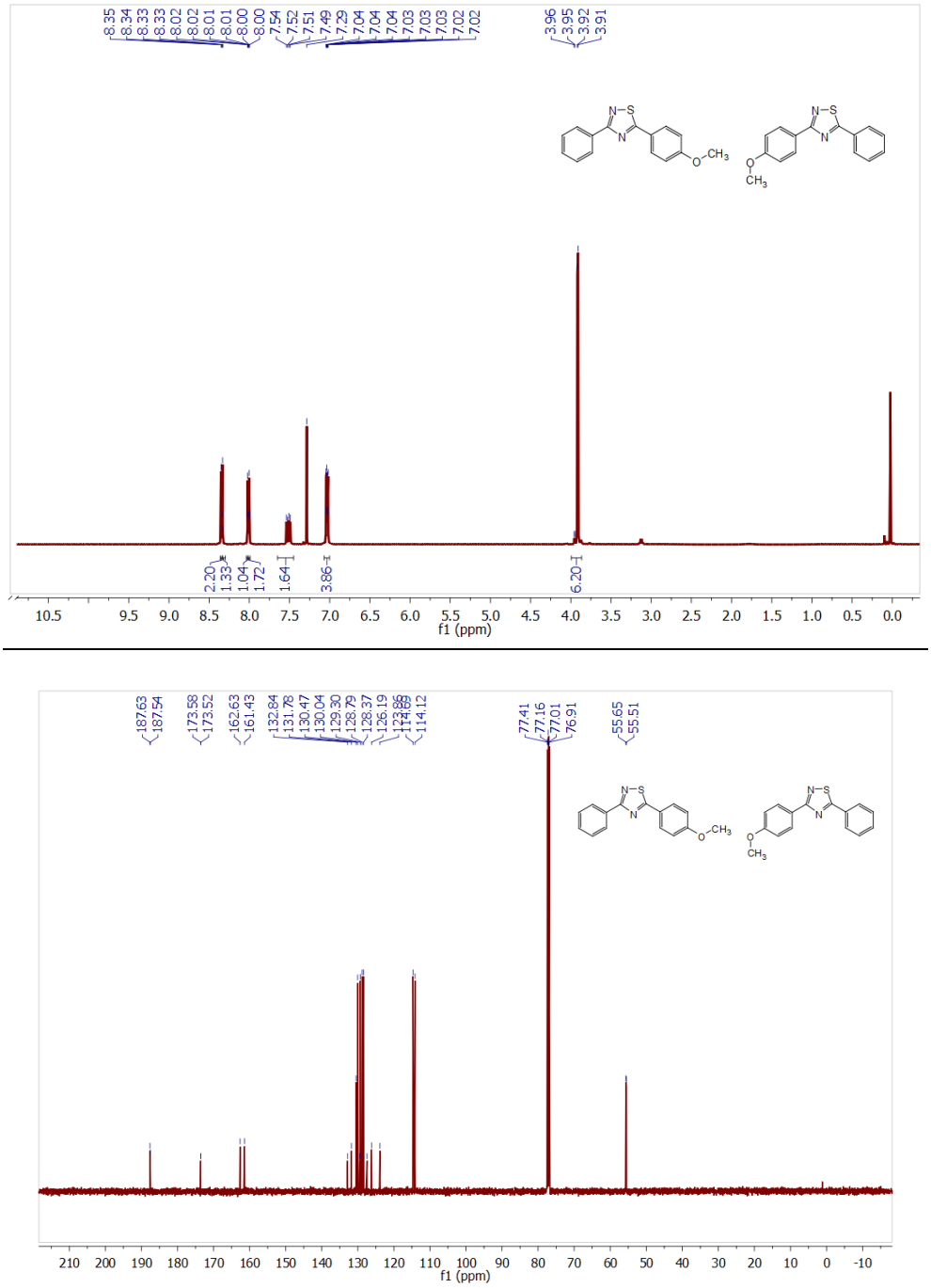


Figure 5.10 ^{1}H & ^{13}C NMR of product **5a & 5b**

5.10 HRMS Spectra

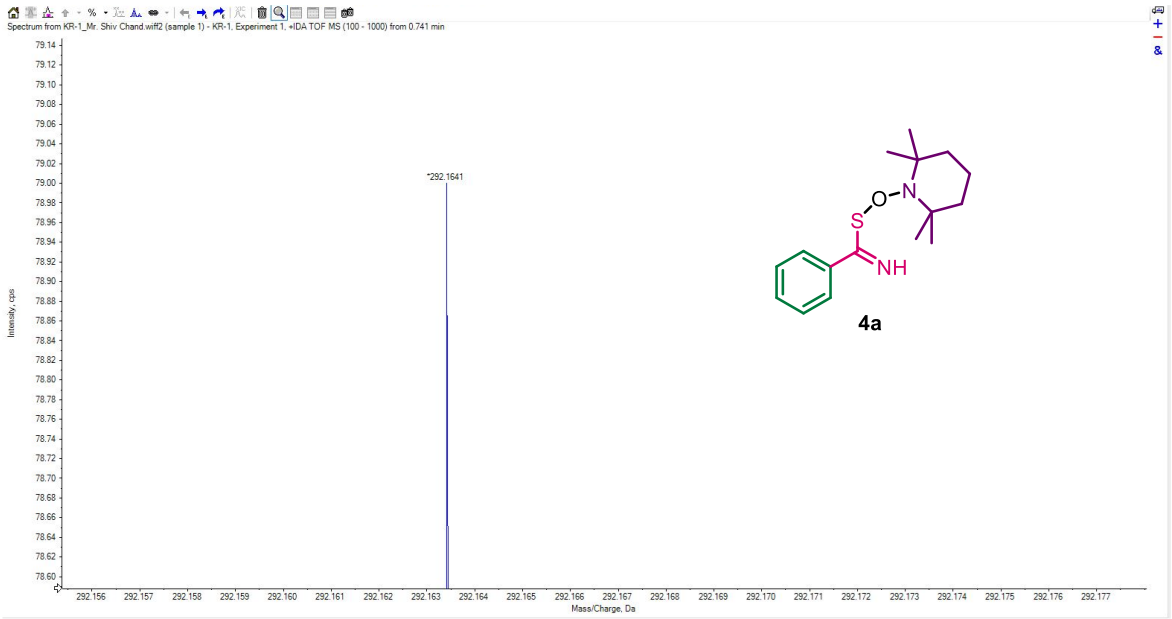


Figure 5.11 HRMS Spectra of **4a**

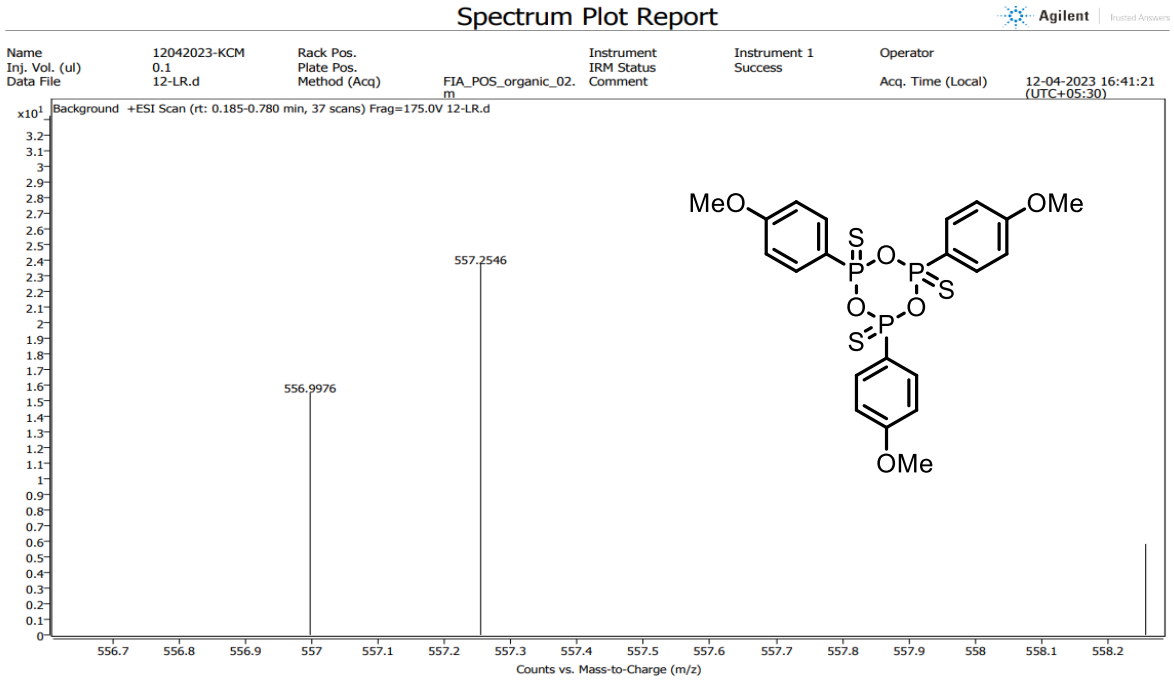


Figure 5.12 HRMS Spectra of **by-product A**

5.11 References

[1] H. Xie, J. Cai, Z. Wang, H. Huang and G.-J. Deng, "A three-component approach to 3, 5-diaryl-1, 2, 4-thiadiazoles under transition-metal-free conditions," *Organic Letter*, **18** (2016) 2196-2199.

[2] Y. Liu, Y. Zhang, J. Zhang, L. Hu and S. Han, "A copper-catalyzed approach for the synthesis of asymmetrical disubstituted 1,2,4-thiadiazoles via elemental sulfur-mediated decarboxylative redox cyclization," *Tetrahedron Letter*, 65 (2021) 152744.

[3] Y.-X. Lu, L.-W. Zhu, T. Lv and B.-H. Chen, "Synthesis of 2, 4-diarylthiazoles throuth palladium-catalyzed cyclization of sulfoxonium ylides and benzothioamide," *Tetrahedron Letter*, **105** (2022) 154051.

[4] Y. Sun, W. Wu and H. Jiang, "Copper (II)-Mediated Homocoupling of Thioamides for the Synthesis of 1, 2, 4-Thiadiazoles," *European. Journal Organic Chemistry*, **2014** (2014) 4239-4243.

[5] Z. Wang, X. Meng, Q. Li, H. Tang, H. Wang and Y. Pan, "Electrochemical Synthesis of 3,5-Disubstituted-1,2,4-thiadiazoles through NH_4I-Mediated Dimerization of Thioamides," *Advance Synthesis Catalyst* **360** (2018) 4043-4048.

[6] L. M. T. Frija, A. J. L. Pombeiro and M. N. Kopylovich, "Building 1, 2, 4-Thiadiazole: Ten Years of Progress," *European. Journal Organic Chemistry*, **2017** (2017) 2670-2682.

[7] G. Vanajatha and V. P. Reddy, "High yielding protocol for oxidative dimerization of primary thioamides: a strategy toward 3, 5-disubstituted 1,2,4-thiadiazoles," *Tetrahedron Letter*, **57** (2016) 2356-2359.

[8] P. C. Patil, D. S. Bhalerao, P. S. Dangate and K. G. Akamanchi, "IBX/TEAB-mediated oxidative dimerization of thioamides: synthesis of 3,5-disubstituted 1,2,4-thiadiazoles," *Tetrahedron Letter*, **50** (2009) 5820-5822.

[9] M. W. Cronyn and T. W. Nakagawa, "The stereochemistry of the Wolff rearrangement," *Journal of American Chemical Society*, **74** (1952) 3693-3693.

[10] H.-Y. Kim, S. H. Kwak, G.-H. Lee and Y.-D. Gong, "Copper-catalyzed synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles via intramolecular N–S bond formation," *Tetrahedron*, **70** (2014) 8737-8743.

[11] Y. Xu, J. Chen, W. Gao, H. Jin, J. Ding and H. Wu, "Solvent-Free Synthesis of 3,5-di(Hetero)Aryl-1,2,4-Thiadiazoles by Grinding of Thioamides under Oxidative Conditions," *Journal of Chemical Research*, **34** (2010) 151-153.

[12] A. Z. Halimehjani, A. Sharifi and H. Rahimzadeh, "**S**imple and Green Procedures for the Synthesis of 3,5-Bis(alkylthio)-1,2,4-thiadiazoles via Oxidative Dimerization of Dithiocarbamates," *Chemistry Select*, **4** (2019) 2634-2638.

[13] S. Chauhan, P. Chaudhary, A. K. Singh, P. Verma, V. Srivastava and J. Kandasamy, "tert-Butyl nitrite induced radical dimerization of primary thioamides and selenoamides at room temperature," *Tetrahedron Letter*, **59** (2018) 272-276.

[14] J. Noei and A. R. Khosropour, "A novel process for the synthesis of 3,5-diaryl-1,2,4-thiadiazoles from aryl nitriles," *Tetrahedron Letter*, **54** (2013) 9-11.

[15] N. X. Hu, Y. Aso, T. Otsubo and F. Ogura, "Polymer-supported diaryl selenoxide and telluroxide as mild and selective oxidizing agents.," *BCSJ*, **59** (1986) 879-884.

[16] S. Chauhan, P. Verma, A. Mishra and V. Srivastava, "An expeditious ultrasound-initiated green synthesis of 1, 2, 4-thiadiazoles in water," *Chemistry Heterocyclic Compounds*, **56** (2020) 123-126.

[17] E. K. Davison and J. Sperry, "Synthesis of the 1, 2, 4-thiadiazole alkaloids polycarpathiamines A and B," *Organic Chemistry Frontiers*, **3** (2016) 38-42.

[18] D. Subhas Bose and K. Raghavender Reddy, "Visible-light promoted serendipitous synthesis of 3,5-diaryl-1,2,4-thiadiazoles *via* oxidative dimerization of thiobenzamides," *Journal of Heterocyclic Chemistry*, **54** (2017) 769-774.

[19] A. D. Shutalev, E. A. Kishko and S. G. Alekseeva, "Reaction of primary thioamides with*p*-toluenesulfinic acid," *Chemistry of Heterocyclic Compounds*, **33** (1997) 352-354.

[20] K. Lee, R. S. Lee and Y. H. Kim, "Highly efficient synthesis of 1,2,4-thiadiazoles from thioamides utilizing tetra(n-butyl)ammonium peroxydisulfate," *Synthetic Communication*, **50** (2020) 1774-1779.

[21] T. Matsuki, N. X. Hu, Y. Aso, T. Otsubo and F. Ogura, Indirect “electrolytic oxidation of thioamides using organotellurium as a mediator.," *BCSJ*, **61** (1988) 2117-2121.

[22] N. Tumula, R. K. Palakodety, S. Balasubramanian and M. Nakka, "Hypervalent Iodine(III)-Mediated Solvent-Free, Regioselective Synthesis of 3,4-Disubstituted 5-Imino-1,2,4-thiadiazoles and 2-Aminobenzo[*d*]thiazoles," *Advance Synthetic Catal*yst," **360** (2018) 2806-2812.

[23] S.-T. Ma, X.-X. Zhu, J.-Y. Xu, Y. Li, X.-M. Zhang, C.-T. Feng and Y. Yan, "Iodide-promoted transformations of imidazopyridines into sulfur-bridged imidazopyridines or 1,2, 4-thiadiazoles," *Chemical Communication*, **57** (2021) 5338-5341.

[24] H. Zali Boeini, *JICS*, "Green Protocol for Synthesis of the 3, 5-disubstituted 1,2,4-thiadiazoles Using N-benzyl-DABCO-tribromide in Aqueous Media," **6** (2009) 547-551.

[25] V. Srivastava, A. Yadav and L. Yadav, "Eosin Y catalyzed visible-light-driven aerobic oxidative cyclization of thioamides to 1, 2, 4-thiadiazoles," *Synlett*, **24** (2013) 465-470.

[26] A. Halimehjani, Y. Nosood, S. Didaran and F. Aryanasab, "Metal-Free Oxidative Dimerization of Dithiocarbamates: Direct Access to 3, 5-Bis-mercapto-1, 2, 4-thiadiazoles" *SynOpen*, **01** (2017) 0138-0142.

[27] J.-W. Zhao, J.-X. Xu and X.-Z. Guo, "Green synthesis of 1, 2, 4-thiadizoles from thioamides in water using molecular oxygen as an oxidant," *Chinese Chemistry Letter*, **25** (2014) 1499-1502.

[28] K. Yajima, K. Yamaguchi and N. Mizuno, "Facile access to 3,5-symmetrically disubstituted 1,2,4-thiadiazoles through phosphovanadomolybdic acid catalyzed aerobic oxidative dimerization of primary thioamides," *Chemical Communication*, **50** (2014) 6748-6750.

[29] A. Yoshimura, C. D. Huss, A. Saito, T. Kitamura and V. V. Zhdankin, 2-“Iodosylbenzoic acid activated by trifluoromethanesulfonic anhydride: Efficient oxidant and electrophilic reagent for preparation of iodonium salts," *New Journal of Chemistry*, **45** (2021) 16434-16437.

[30] L. Rubab, A. Anum, S. A. Al-Hussain, A. Irfan, S. Ahmad, S. Ullah, A. A. Al-Mutairi and M. E. Zaki, "Green chemistry in organic synthesis: Recent update on green catalytic approaches in synthesis of 1, 2, 4-thiadiazoles," *Catalysts*, **12** (2022) 1329.

[31] R. N. Suresh, T. R. Swaroop, V. G. Shalini, K. Mantelingu and K. S. Rangappa, "Synthesis of 3, 5-bis (acyl)-1, 2, 4-thiadiazoles via iodine mediated oxidative dimerization of α-oxothioamides," *Tetrahedron Letter*, **116** (2023) 154302.

[32] A. P. Zarecki, J. L. Kolanowski and W. T. Markiewicz, "Microwave-assisted catalytic method for a green synthesis of amides directly from amines and carboxylic acids," *Molecules*, **25** (2020) 1761.

[33] P. Sureshbabu, S. Azeez, P. Chaudhary and J. Kandasamy, "tert-Butyl nitrite promoted transamidation of secondary amides under metal and catalyst free conditions," *Organic & Biomolecular Chemistry*, **17** (2019, 845-850.

[34] N. Fattahi, M. Ayubi and A. Ramazani, "Amidation and esterification of carboxylic acids with amines and phenols by N,N′-diisopropylcarbodiimide: A new approach for amide and ester bond formation in water," *Tetrahedron*, **74** (2018) 4351-4356.

[35] Y.-L. Zheng and S. G. Newman, "Methyl esters as cross-coupling electrophiles: Direct synthesis of amide bonds," *ACS Catalayst*, **9** (2019) 4426-4433.

[36] Z. Li, X. Tang, Y. Jiang, M. Zuo, Y. Wang, W. Chen, X. Zeng, Y. Sun and L. Lin, "Tandem thionation of biomass derived levulinic acid with Lawesson's reagent," *Green Chemistry*, **18** (2016) 2971-2975.

[37] A. Mishra, S. Chauhan, P. Verma, S. Singh and V. Srivastava, "TBHP-Initiated Transamidation of Secondary Amides via C− N Bond Activation: A Metal-Free Approach" *Asian Journal of Organic Chemistry*, **8** (2019) 853-857.

[38] S. Chauhan, P. Verma, J. Kandasamy and V. Srivastava, "Visible-Light-Induced Tandem Radical Brominative Addition/Cyclization of Activated Alkynes with CBr_4 for the Synthesis of 3-Bromocoumarins," *Chemistry Select*, **5** (2020) 9030-9033.

[39] J. Bai, J. Huang, Q. Jiang, Y. Li, H. Wang, H. Yu, Q. Zhang, Y. Cao and F. Peng, "Radical Propagation Facilitating Aerobic Oxidation of Substituted Aromatics Promoted by *tert*-Butyl Hydroperoxide," *Chemistry Select* **6** (2021) 6895-6903.

[40] C. Guan, J. Ji, Z. Li, Q. Wei, X. Wu and S. Liu, "Facile synthesis of N_2-substituted-1, 2, 3-triazole from aryl ethynylene and azide via a one-pot two-step strategy," *Tetrahedron*, **108** (2022) 132-670.

[41] A. Sumita, J. Lee, Y. Otani and T. Ohwada, "Facile synthesis of 2, 3-benzodiazepines using one-pot two-step phosphate-assisted acylation–hydrazine cyclization reactions," *Organic & Biomolecular Chemistry*, **16** (2018) 4013-4020.

[42] P. Chaudhary, S. Gupta, N. Muniyappan, S. Sabiah and J. Kandasamy, "An efficient synthesis of **N**-nitrosamines under solvent, metal and acid free conditions using tert-butyl nitrite," *Green Chemistry*, **18** (2016) 2323-2330.

[43] V. Singh, K. Rajput, A. Mishra, S. Singh and V. Srivastava, "Microwave-assisted chemoselective transamidation of secondary amides by selective N–C (O) bond cleavage under catalyst, additive, and solvent-free conditions," *Chemical Commun*ication **59** (2023) 14009-14012