Chapter 4

Synthesis of Thioamides from Amides Using Lawesson Reagent in Solvent-Free Conditions: A Chromatography-Free Approach

4.1 Introduction

Sulfur-containing compounds, especially thiocarbonyls, are highly versatile intermediates or precursors that find many applications both in synthetic and biological chemistry [1]. Thioamides are important building blocks; as they are applied broadly in the areas of synthesis of many significant sulfur-containing heterocycles, such as thiazolines, thiazoles, thiazolinones, thiadiazoles, tetrazoles, mesoionic rhodanine, betaines and other heterocyclic [2–9].

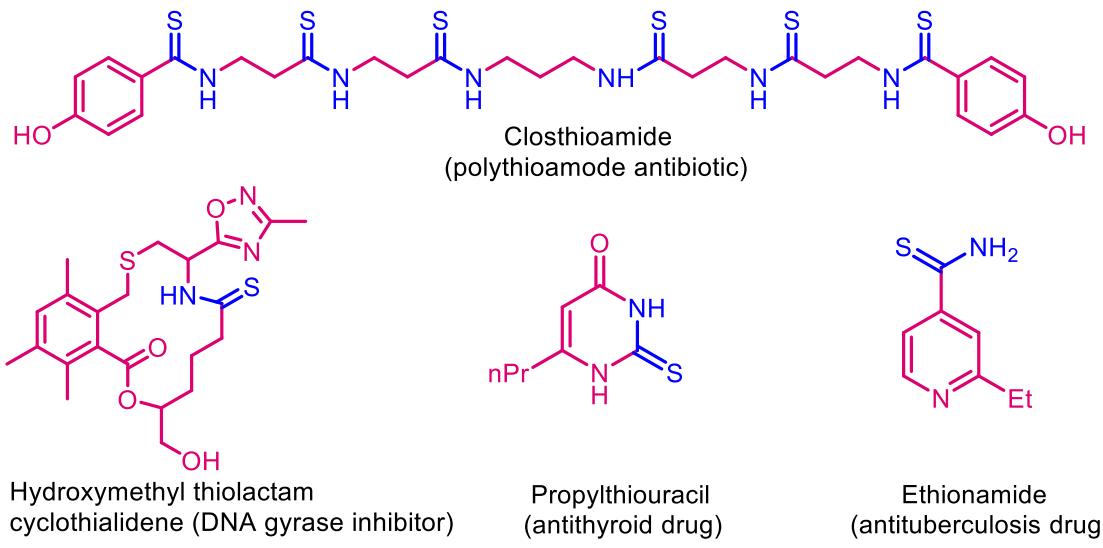


Figure 4.1 Representative bioactive thioamide scaffolds.

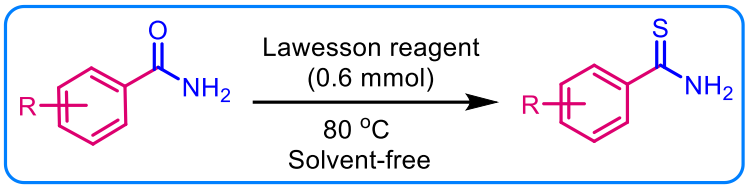
There are many medicinal applications of thioamide functional groups, including antifungal and antibacterial agents [10, 11], as well as the treatment of diseases such as tuberculosis and leprosy. Ethion-amide is employed as a second-line treatment when the disease shows resistance to other antibiotics [12]. It has found widespread applications in many synthetically useful transformations, and their derivatives have attracted considerable attention because of their utility in the synthesis of a variety of biologically and pharmaceutically relevant moieties such as Ethion-amide, propylthiouracil, closthioamide, hydroxymethyl thiolactam cyclothialidine, and ncyclo-hexylethyl-ETAsV [13], etc. (**Figure 4.1**).

Organic chemists for many years have been interested in the conversion of the carbonyl group into thiocarbonyl group. Among the various procedures available for the synthesis of thioamides, the most general one involves the thionation of amides and nitriles using sulfur-transfer reagents, such as Lawesson reagent [14–16], P_4S_{10} [17], $(NH_4)_2S$ [18, 19], $(TMS)_2S$ [20], S_8 [21], $PSCl_3$ [22]. Hye Young Jang, et al. reported the aerobic oxidation of thiols by using the metal catalyst $CuCl_2$, base TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene), oxidant O_2 (under 1-atmosphere nitrogen) in toluene at 100 ^oC in 18 h [23]. Nguyen, T. B. et al. have reported the oxidative coupling of two different aliphatic primary amines into thioamides by elemental sulfur under solvent-free conditions at 130 ^oC [24]. In 2018 A. Savateev et al., reported that thioamide synthesis using potassium poly(heptazineimide), a carbon nitride based photocatalyst, effectively promotes

the Kindler reaction under visible light irradiation [25]. C. Oliver Kappe, et al. [27] reported the synthesis of thioamides via Kindler reaction with a three-component condensation reaction of aldehydes, amines, and elemental sulfur using 1-methyl-2-pyrrolidone (NMP) as a solvent employing microwave flash heating at 110-180 ^{o}C for 2-20 min. In literature, thioamide is synthesized from nitrile involving thioacetic acid in the presence of calcium hydroxide [28], gaseous H_2S in the presence of anion-exchange resin (Dowex 1X8, SH-form) [29], microwave-assisted solvent-free [30] NaSH and $MgCl_2$ in DMF [31] sodium hydrogen sulfide and diethylamine [32]. Verma et al. [33] have reported microwave-induced synthesis under solvent-free conditions, and Kotyk et al. [34] have reported mechanochemical grinding methods under solvent-free conditions, but both methods required chromatographic separations. X. Hu, reported chromatography-free synthesis, but the reaction was carried out in solvent and took longer reaction time [35]. The disadvantages of some of the synthetic strategies include the use of metal catalysts, expensive reagents, longer reaction times, use of environmentally hazardous organic solvents, harsh reaction conditions, a tedious work-up procedure, and low yields, besides this all the reported methods required chromatography to obtain the pure compounds [36-38]. Therefore, the development of a facile, metal-free, efficient, and environmentally friendly method is still in demand.

In continuation of research work, we have developed a metal-free, efficient, facile, and oxidant-free protocol for the synthesis of thioamide derivatives by using the

environmentally safe, amide/ nitriles and Lawesson reagent in solvent-free conditions, and the pure compounds have been obtained without chromatographic separation it requires plenty of solvents that affect the economic and environments (**Scheme 4.1**).



✓Metal catalyst-synthesis ✓Green synthesis ✓Chromatography-free ✓Cost effective

Scheme 4.1 Synthesis of thioamides.

Amides are cheap and naturally abundant materials reported for their use as key starting materials in various organic syntheses. On the other hand, Lawesson reagent (LR) is an omni-available, low-priced, and powerful versatile thionating reagent for C-S bond formation. In recent years, with the increase in environmental awareness with respect to green chemistry, there is also a pressing need to develop eco-friendly approaches for the preparation of various chemicals. There has been developing stress on the exploitation and design of environment-friendly solvent-free reactions to reduce the amount of toxic waste arising from chemical processes stimulated by inflexible environment protection laws [39,40]. Due to the emergent concern for the influence of organic solvents on the environment as well as on the human body, organic reactions without the use of conventional organic solvents have attracted the attention of synthetic organic chemists.

Although some modern solvents, such as ionic liquids and water, have been extensively studied recently, not using a solvent at all is absolutely the best option. The development of solvent-free organic reactions is thus gaining prominence because solvent-free reactions not only reduce environmental pollution but are also high-yielding and cost-effective.

4.2 Results and Discussion

4.2.1 Optimization of The Reaction Conditions

At the beginning of our study, the reaction between amide/nitrile **1a** (1.0 mmol) and Lawesson reagent (0.6 mmol) was carried out as the model substrate for the synthesis of the desired product **2a**. This included different parameters like solvent, temperature, and molar ratio of the reactant (**Table 4.1**). First of all, the model reaction was carried out in different non-polar and polar solvents. In non-polar solvents toluene, benzene at its boiling temperature in 1h gave the product **2a** in 45, 50% yield respectably (**Table 4.1, entries 1-2**), and in the case of polar aprotic solvents like tetrahydrofuran, dichloromethane, acetonitrile, at its refluxed temperature gave the product **2a** but no satisfactory yield was obtained (**Table 4.1, entries 3-5**). Then we examined polar protic solvents like, methanol, ethanol, and water failed to give the desired product **2a** (**Table 4.1, entries 6-8**).

Then the reaction was carried out in solvent-free conditions. To our enchantment, the yield was improved significantly, and it gave 85% yield in 25 min at 80 ^{o}C when the reaction was performed without solvent (**Table 4.1, entry 9**). Solvent-free conditions increase the rate of reaction due to an increase in collision frequency, which results in a

decrease in the reaction time; this could be the reason which resulted in high yield in solvent-free conditions. Next, other factors, such as temperature and amount of the Lawesson reagent, were also evaluated. Increasing the reaction temperature above 80 ^{o}C didn't have a significant effect on the yield of **2a** (**Table 4.1, entries 10-11**). Whereas on decreasing the temperature the yields of our desired product **2a** also decrease (**Table 4.1, entry 12**). It is important to mention that the reaction temperature affects the yield of the product and increases the amount of Lawesson reagent with no significant effect on the yield of **2a** (**Table 4.1, entries 13-14**). Therefore, the optimized conditions selected for thioamides **2a** synthesis were amide **1a** (1.0 mmol), and Lawesson reagent (0.6 mmol) at 80 ^{o}C without solvent.

The reactions involving the LR reagent have formed a six-membered ring byproduct A (**Figure 4.2**) [41,42].

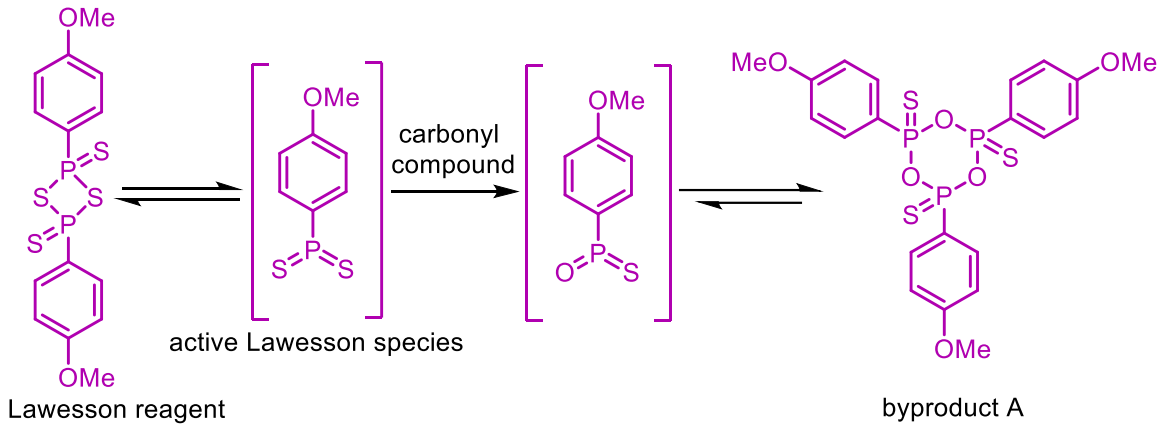
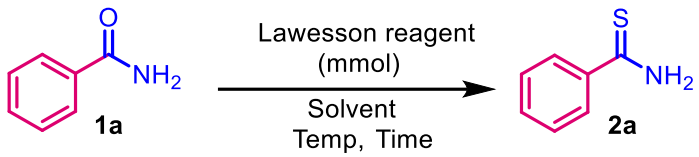


Figure 4.2 Representative six-membered by-products A.

After completion of the reaction, the mixture was kept aside at room temperature and diluted with ethyl acetate, and the undissolved byproduct **A** was isolated by filtration. The byproduct **A** was recrystallized from benzene and confirmed by its melting point and HRMS spectral data. In workup procedures, it is generally insoluble in ethyl acetate and separated by simple filtrations. Furthermore, byproduct **A** was recrystallized from benzene and confirmed by melting point and HRMS data [43]. To obtain the desired product (**2a**), the solvent ethyl acetate was removed under reduced pressure giving the yellow residue, which was recrystallized from ethanol, and pure (**2a**) was obtained in 83% yield without any chromatographic separation. The final product **2a** was characterized for its molecular structure and composition by spectral data ^{1}H, ^{13}C NMR spectral analysis.

Table 4.1 Optimization of the Lawesson reagent, solvent, temperature, and time for the synthesis of thioamide 2a[a]

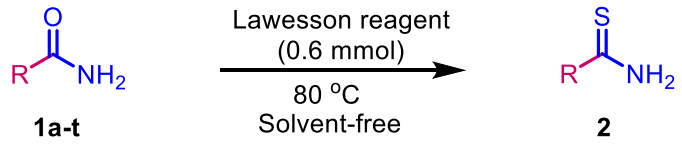


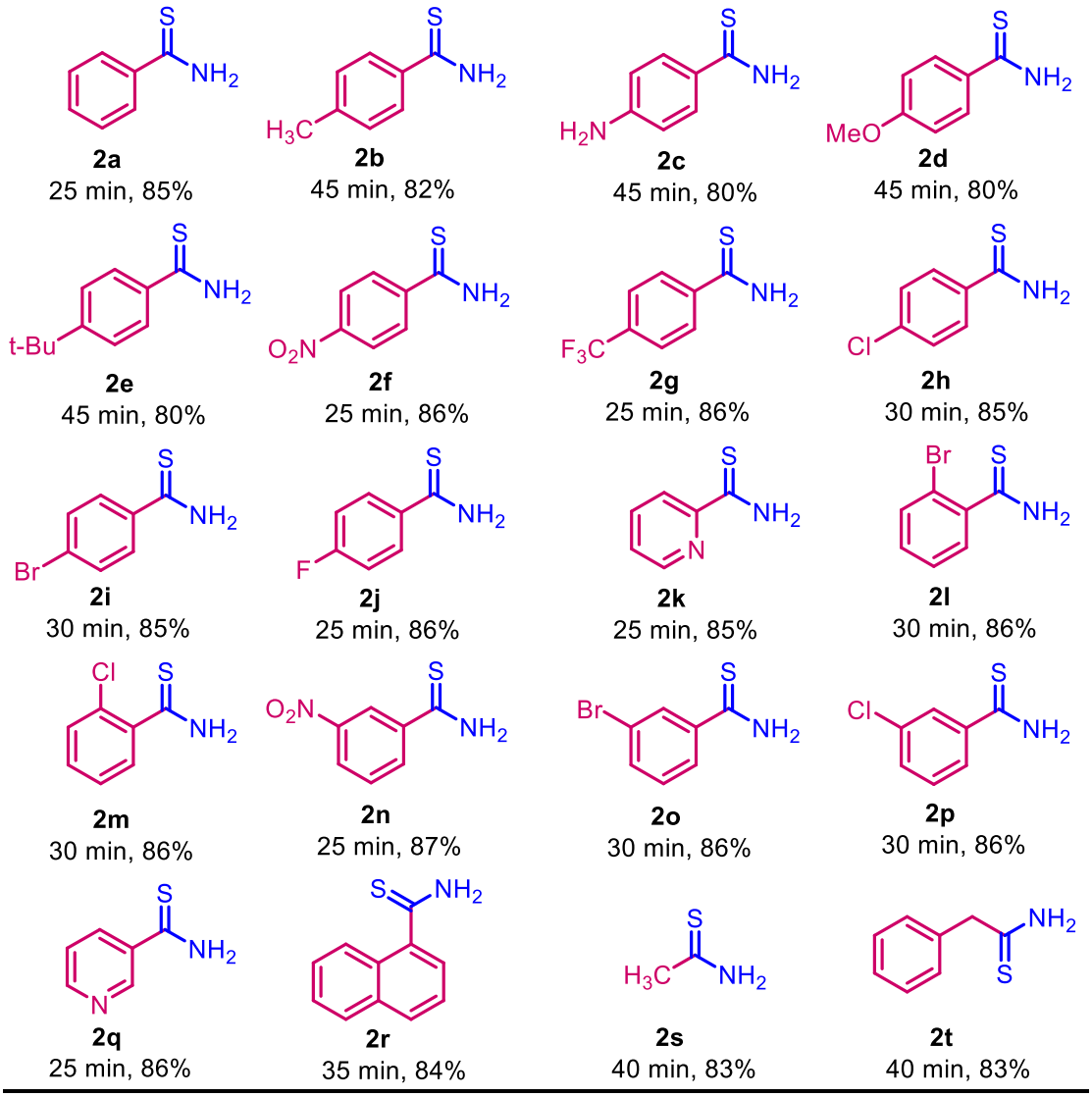
S.No	Solvent	LR (mmol)	Temp (°C)	Time (min)	Yield (%)[b]
1	Toluene	0.6	Reflux	60	50
2	Benzene	0.6	Reflux	60	45
3	THF	0.6	Reflux	60	40
4	DCM	0.6	Reflux	60	35
5	Acetonitrile	0.6	Reflux	60	40
6	Methanol	0.6	Reflux	60	n.r
7	Ethanol	0.6	Reflux	60	n.r
8	Water	0.6	Reflux	60	n.r
9	Solvent-free	0.6	80	25	85
10	Solvent-free	0.6	90	25	86
11	Solvent-free	0.6	100	25	87
12	Solvent-free	0.6	75	25	52
13	Solvent-free	1.0	80	25	85
14	Solvent-free	1.0	70	25	55

[a] Reaction conditions: amide (1.0 mmol), Lawesson reagent (0.6 mmol) at 80 °C.
[b] Isolated yield.

Encouraged by these results, we next studied the substrate scope of this reaction. A series of thioamides were synthesized in good to excellent yields under the optimized reaction conditions, and representative results are listed in (**Scheme 4.2**). Both electron-donating and electron-withdrawing groups are compatible for this reaction. It was found that electron-donating substituents such as required longer reaction time (**Scheme 4.2**), as the electron-donating substituent amide decreases the electrophilic character of amide. The electron-withdrawing substituent-containing amides required a shorter reaction time as compared to electron-donating substituent-containing amides. Notably, the reaction of heterocyclic amides, such as pyridine-2-thiocarboxamide and thionictoniamide, also proceeded smoothly to provide the thioamide in moderate yields (**Scheme 4.2, 2k, 2q**). The scope of the above established methodology was also evaluated with various tertiary amides derivatives (**Scheme 4.3**) and nitriles derivatives (**Scheme 4.4**) for obtaining thioamide products. The outcomes showed favorable results with good yield values.

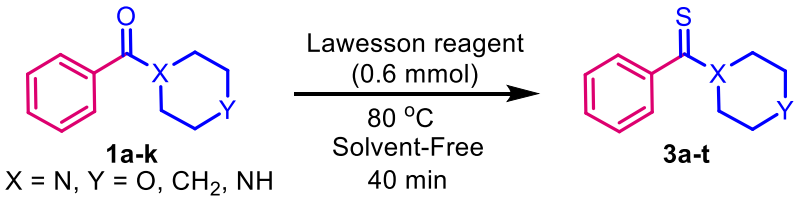
Scheme 4.2 Substrate scope with various primary amides[a]

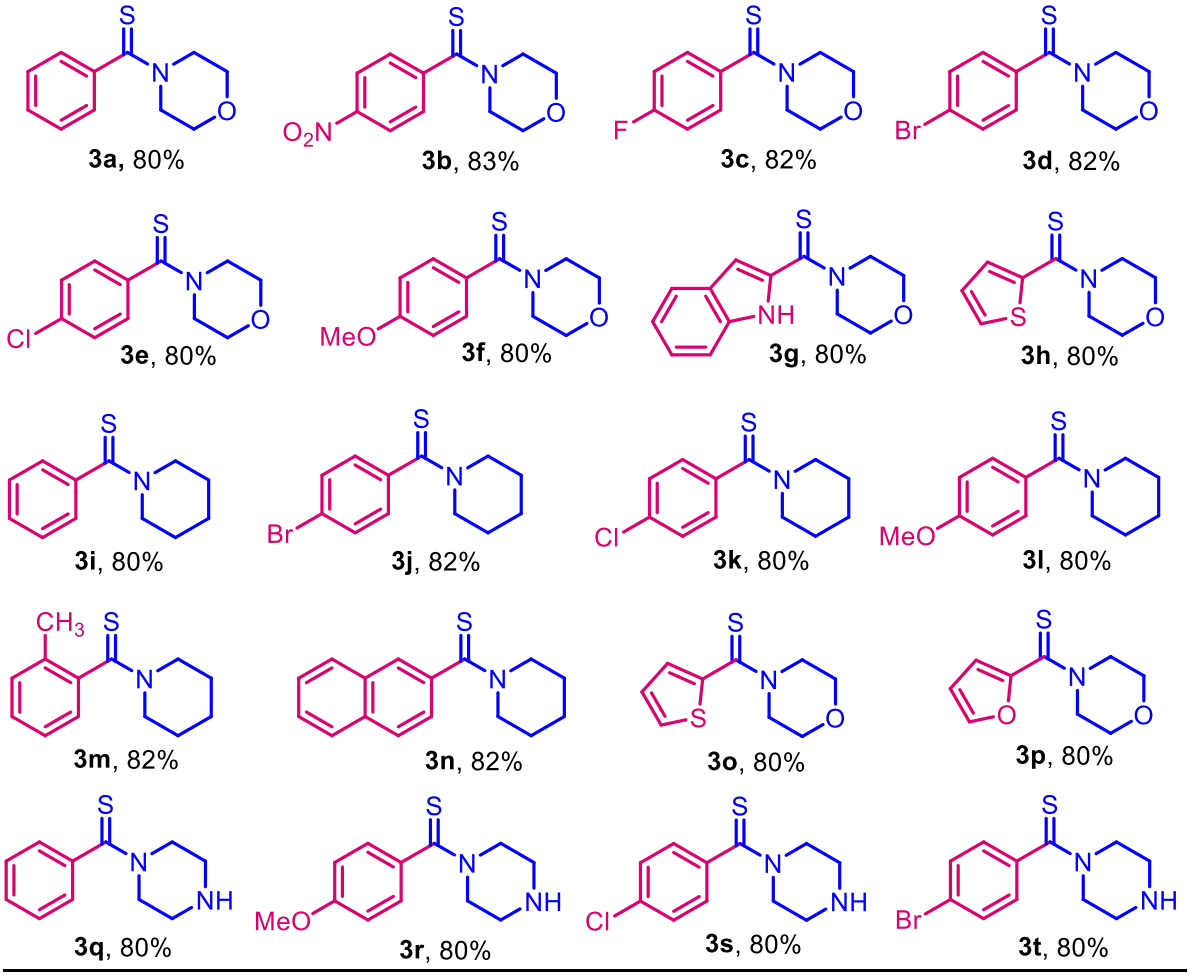




[a] Reaction conditions: amide (1.0 mmol), Lawesson reagent (0.6 mmol) at 80 °C
[b] Isolated yield.

Scheme 4.3 Substrate scope with various secondary/tertiary amides[a]

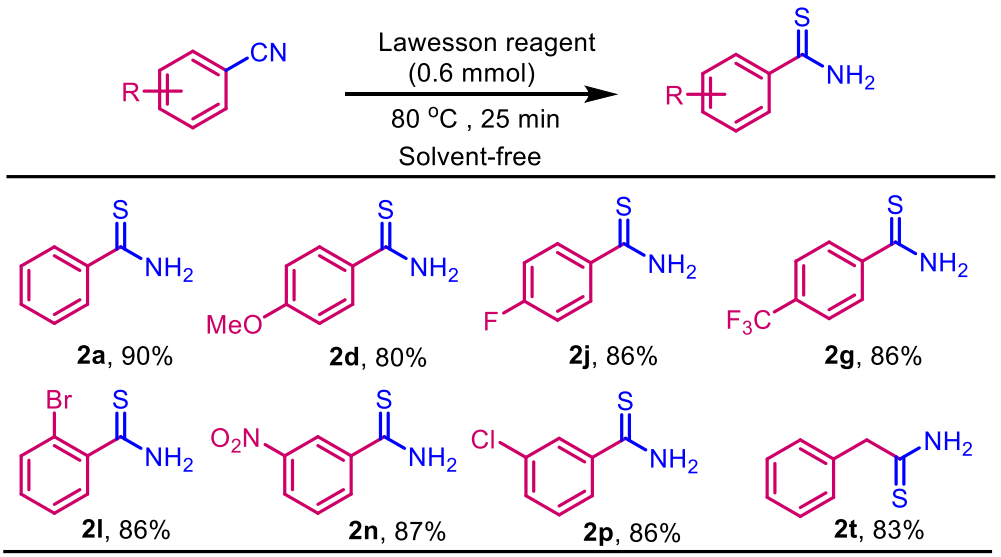




[a] Reaction conditions: amide (1.0 mmol), Lawesson reagent (0.6 mmol), at 80 °C.

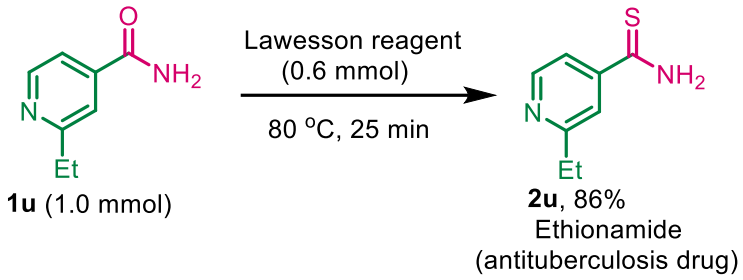
[b] Isolated yield.

Scheme 4.4 Substrate scope with various benzonitrile[a]



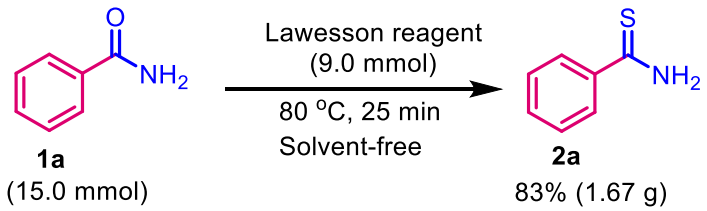
[a] Reaction conditions: benzonitrile (1.0 mmol), Lawesson reagent (0.6 mmol) at 80 °C. [b] Isolated yield.

Scheme 4.5 Synthesis of Ethionamide



After exploring the scope of this methodology, we attempted to synthesize ethinamide, a promising antituberculosis drug designed to work by stopping the growth of bacteria and treating tuberculosis (TB) in the body using the developed method. The reaction of 2-ethylisonicotinamide **1u** (1.0 mmol) with LR (0.6 mmol) gave the desired product **2u** in 86% yield (**Scheme 4.5**).

4.2.2 Gram-scale synthesis protocol for thiobenzamide (2a)



Scheme 4.6 Synthesis of **2a** on gram-scale.

To validate the prospective synthetic application of the established methodology for thiobenzamide (**2a**), the experiment was conducted on a gram scale using amide (**1a**) (15.0 mmol, 1.0 equiv.), Lawesson reagent (9.0 mmol, 0.6 equiv) under optimized reaction conditions (**Scheme 4.6**) gave an 83% yield of (**2a**). The experimental work showed a robust and acceptable gram-scale method for the synthesis of thiobenzamide (**2**).

4.3 Proposed mechanism

On the basis of the experimental and previous reports, a proposed mechanism for synthesizing the thioamide reaction is shown in (**Figure 4.4**) [44]. Lawesson reagent has a four-membered ring of alternating sulfur and phosphorus atoms. The central phosphorus-sulfur four-membered ring dissociates to form two reactive dithiophosphine species. The reactive species dithiophosphine ylide reacts with benzamide **1a** and gives thioxaphosphenate intermediate **A**; 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. The mechanism

may involve activating the amide group by complexation with Lawesson reagent followed by nucleophilic addition to produce thioamide.

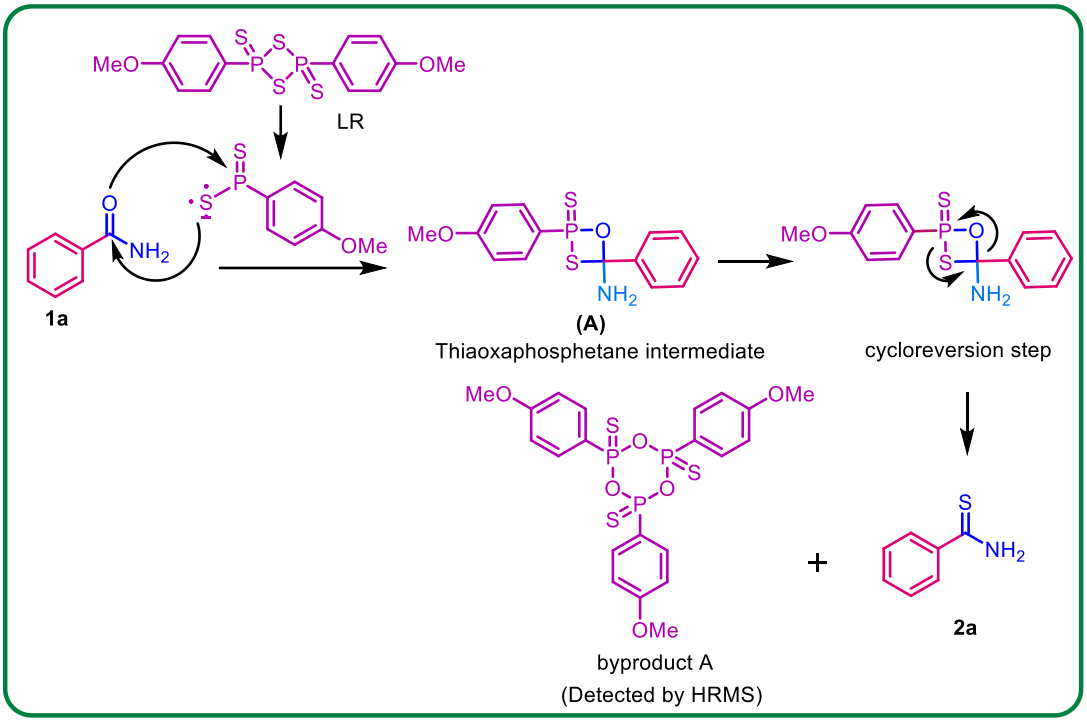


Figure 4.3 Probable reaction mechanism.

4.4 Conclusion

In conclusion, a highly efficient and practical method for synthesizing a series of biologically interesting thioamide derivatives has been developed from Lawesson reagents in solvent-free conditions. The cheap and readily available LR acted as the sulfur source to assemble the thioamide derivatives that do not require any acidic or basic media. This reaction represents adequate access to thioamides from readily available starting materials

with good functional group tolerance. The prominent advantages of this method are shorter reaction time, chromatography-free, and easy work-up.

4.5 Experimental Section

4.5.1 General Procedure for the Synthesis of Thioamides

An oven-dried round bottom flask (25 ml) equipped with a stir bar was charged with amide/nitrile (1.0 mmol), and Lawesson reagent (0.6 mmol). The reaction mixture was heated at 80 ^{o}C, and TLC monitored the progress of the reaction. After completion of the reaction, the mixture was cooled at room temperature; the solid was dissolved with ethyl acetate and undissolved byproduct **A** was isolated by filtration. Byproduct **A** was recrystallized from benzene and confirmed by melting point and mass spectra. The solvent ethyl acetate was removed under reduced pressure, and the yellow residue was recrystallized from ethanol to obtain the pure product (**2a**). All the products were characterized based on ^{1}H-NMR, ^{13}C-NMR, and HRMS spectral data.

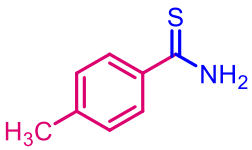
4.6 Analytical data for [2a-2t, 3a-3t]

Thiobenzamide (**2a**)

yield 90%; Yellow crystalline solid; m.p. 116-127 ^{o}C; **^{1}H NMR** (500 MHz, DMSO-d_6); δ 9.87 (s, 1H), 9.51 (s, 1H), 7.87-7.98 (m, 2H), 7.52-7.49 (m, 1H), 7.43-7.40 (m, 2H) ppm.

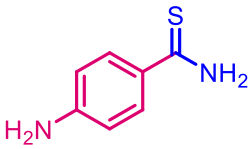
^{13}C NMR (126 MHz, DMSO-d_6); δ 200.6, 139.9, 131.5, 128.3, 127.7 ppm. HRMS ESI $[M+H]^+$ calculated for C_7H_7NS 138.0299; found: 138.0294

4-Methylthiobenzamide (**2b**)



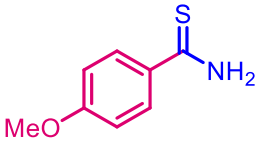
Yellow Crystalline solid; yield 90%; m.p. 167-168 °C; **^{1}H NMR** (500 MHz, DMSO-d_6); δ 9.76 (s, 1H), 9.42 (s, 1H), 7.82-7.81 (d, 2H), 7.23-7.21 (d, 2H), 2.33 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6); δ 200.2, 141.8, 136.9, 128.9, 127.8, 21.3, HRMS (ESI) m/z: [M+H] + calculated for C_8H_9SN 152.0455; found: 152.0450

4-Aminothiobenzamide (2c)



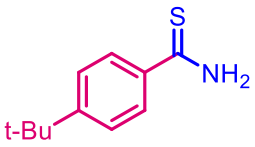
Yellow Crystalline solid; yield 90%; m.p. 187-188 °C; **^{1}H NMR** (500 MHz, DMSO-d_6); δ 9.16 (s, 1H), 8.96 (s, 1H) 7.79-7.77 (d, 2H), 6.51-6.49 (d, 2H), 5.83 (s, 2H); **^{13}C NMR** (126 MHz, DMSO-d_6); δ 198.4, 1528, 130.1, 125.8, 112.4, HRMS (ESI) m/z: [M+H]+ calculated for C_7H_8SN2 153.0408; found: 153.0406

4-Methoxythiobenzamide (2d)



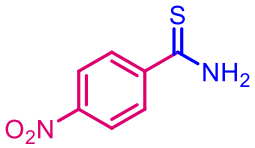
Yellow Crystalline solid; yield 90%; m.p. 154-155 °C; **^{1}H NMR** (500 MHz, DMSO-d_6); δ 9.76 (s, 1H), 9.41 (s, 1H), 7.84-7.82 (d, 2H), 7.23-7.21 (d, 2H), 3.33 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6); δ 200.1, 141.7, 137.0, 128.8, 127.8, 21.3, HRMS (ESI) m/z: $[M+H]^+$ calculated for C_8H_9NOS 168.0405; found: 168.0401.

4-t-butylthiobenzamide (2e)

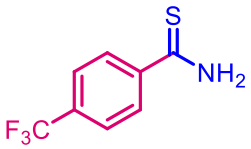


Yellow Crystalline solid; yield 90%; m.p. 145-147 °C; **^{1}H NMR**: (500 MHz, DMSO-d_6); δ 9.77 (s, 1H), 9.42 (s, 1H), 7.84 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 1.29 (s, 9H). **^{13}C NMR** (126 MHz, DMSO-d_6); δ 200.3, 154.5, 137.2, 127.6, 125.1, 35.0, 31.3, HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{11}H_{15}NS$ 194.0925; found: 194.0920.

4-Nitrothiobenzamide (2f)

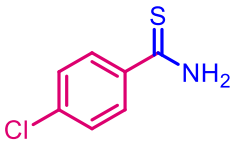


Yellow solid; yield 90%; m.p. 155-157 °C; **^{1}H NMR** (500 MHz, DMSO-d_6); δ 10.23 (s, 1H), 9.82 (s, 1H), 8.27-8.24 (m, 2H), 8.04–8.01 (m, 2H), **^{13}C NMR** (126 MHz, DMSO-d_6); δ 198.8, 149.0, 149.6, 128.8, 123.6, HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_7H_6SNO_2$ 169.0119; found: 169.0113.



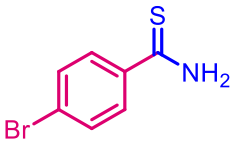
Yellow Crystalline solid; yield 90%; m.p. 134-136 °C; **^{1}H NMR** (500 MHz, DMSO-d_6); δ 10.12 (s, 1H), 9.73 (s, 1H), 8.00-7.98 (d, 2H), 7.80-7.78 (d, 2H), **^{13}C NMR** (126 MHz, DMSO-d_6); δ 199.4, 143.8, 137.8, 128.3, 125.4, 124.4, HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_8H_6SNF_3$ 206.0173; found: 206.0170

4-Chlorothiobenzamide (2h)



Yellow Crystalline solid; yield 90%; m.p. 131-133 °C; **^{1}H NMR** (500 MHz, DMSO-d_6); δ 9.95 (s, 1H), 9.57 (s, 1H), 7.92-7.90 (d, 2H), 7.50-7.48 (d, 2H), **13C NMR** (126 MHz, DMSO-d_6) δ 199.1, 138.5, 136.5, 129.5, 128.3, HRMS (ESI) m/z: $[M+H]^+$ calculated for C_7H_6ClNS 171.9909; found: 171.9905

4-Bromothiobenzamide(2i)

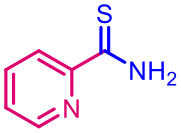


Yellow Crystalline solid; yield 90%; m.p. 140-142 °C; **^{1}H NMR** (500 MHz, DMSO-d_6); δ 9.95 (s, 1H), 9.57 (s, 1H), 7.92-7.90 (d, 2H), 7.50-7.48 (m, 2H), **^{13}C NMR** (126 MHz, DMSO-d_6) δ 199.1, 138.5, 136.5, 129.5, 128.3, HRMS (ESI) m/z: $[M+H]^+$ calculated for C_7H_6BrNS 215.9404; found: 215.9409

4-Fluorothiobenzamide (2j)

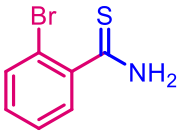
Yellow solid; yield 90%; m.p. 145-147 °C; **^{1}H NMR** (500 MHz, DMSO-d_6); δ 9.89 (s, 1H), 9.51 (s, 1H), 8.51 -7.96 (m, 2H), 7.27- 7.24 (m, 2H), **^{13}C NMR** (126 MHz, DMSO-d_6); δ 199.0, 165.3, 136.3, 130.9, 115.2, HRMS (ESI) m/z: [M+H] + calculated for C_7H_6FSN 156.0205; found: 156.0201

2-Pyridinecarbothioamide (2k)



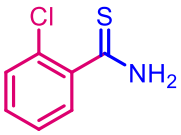
Yellow solid; yield 90%; m.p. 136-137 °C; **^{1}H NMR** (500 MHz, DMSO-d_6); δ 10.17 (s, 1H), 9.93 (s, 1H), 8.59 (m, 1H), 8.53-8.51 (d, 1H) 7.98-7.95 (d, 1H), 7.59-7.57 (m, 1H), **^{13}C NMR** (126 MHz, DMSO-d_6); δ 195.1, 152.1, 148.0, 137.8, 126.7, 125.0, HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_6H_6N_2S$ 139.0251; found: 139.0258

2-Bromothiobenzamide (2l)



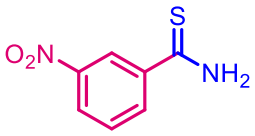
Yellow solid; yield 90%; m.p. 197-199 °C; **^{1}H NMR** (500 MHz, DMSO-d_6); δ 10.12 (s, 1H), 9.66 (s, 1H), 7.61 (m, 1H), 7.40-7.37 (d, 1H) 7.35-7.33 (d, 1H), 7.28-7.25 (m, 1H), **^{13}C NMR** (126 MHz, DMSO-d_6;) δ 201.5, 145.0, 132.9, 130.2, 128.5, 127.9, 117.4, HRMS (ESI) m/z: $[M+H]^+$ calculated for C_7H_6BrSN 215.9404; found: 215.9409

2-Chlorothiobenzamide (2m)



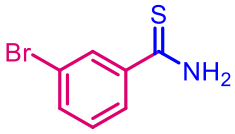
Yellow Crystalline solid; yield 90%; m.p. 67 °C; **^{1}H NMR** (500 MHz, DMSO-*d6*); δ 10.17 (s, 1H), 9.69 (s, 1H), 7.46-7.34 (m, 4H), **^{13}C NMR** (126 MHz, DMSO-d_6); δ 201.1, 143.0, 130.1, 129.7, 128.7, 128.0, 127.3, HRMS (ESI) m/z: $[M+H]^+$ calculated for C_7H_6ClNS 171.9909; found: 171.9913.

3-Nitrothiobenzamide (2n)



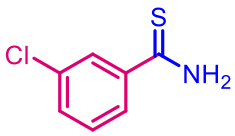
Yellow Crystalline solid; yield 90%; m.p. 130-131 °C; **^{1}H NMR** (500 MHz, DMSO-*d_6*); δ 10.21 (s, 1H), 9.86 (s, 1H), 8.71-8.70 (s, 1H), 8.34-8.28 (d, 2H) 7.74-7.71 (m, 1H), **^{13}C NMR** (126 MHz, DMSO-*d_6*); δ 197.8, 147.7, 141.1, 133.5, 130.1, 125.9, 122.6, HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_6H_6N_2SO_2$ 171.0150; found: 171.0153.

3-Bromothiobenzamide (2o)



Yellow Crystalline solid; yield 90%; m.p. 106-107 °C; **^{1}H NMR** (500 MHz, DMSO-*d_6*); δ 10.03 (s, 1H), 9.62 (s, 1H), 7.90-7.82 (m, 2H), 7.59-7.58 (m, 1H) 7.57-7.44 (m, 1H), **^{13}C NMR** (126 MHz, DMSO-*d6*); δ 198.8, 141.7, 133.1, 131.2, 130.3, 127.4, 126.3, HRMS (ESI) m/z: $[M+H]^+$ calculated for C_6H_6BrNS 203.9404; found: 203.9401

3-Chlorothiobenzamide (2p)



Yellow solid; yield 90%; m.p. 107-108 °C; **^{1}H NMR** (500 MHz, DMSO-*d_6*); δ 10.01 (s, 1H), 9.62 (s, 1H), 7.86-7.82 (m, 2H), 7.59-7.58 (m, 1H) 7.57-7.44 (m, 1H), **^{13}C NMR** (126 MHz, DMSO-*d6*); δ 198.8, 141.7, 133.1, 131.2, 130.3, 127.4, 126.3, HRMS (ESI) m/z: $[M+H]^+$ calculated for C_6H_6ClNS 159.9909; found: 159.9912.

3-Pyridinecarbothioamide (2q)

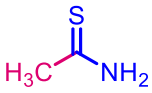
Yellow solid; yield 90%; m.p. 117-118 °C; **^{1}H NMR** (500 MHz, DMSO-*d_6*); δ 10.07 (s, 1H), 9.73 (s, 1H), 9.00 (s, 1H), 8.66-8.65 (d, 1H), 8.20-8.19 (d, 1H). 7.46-7.44 (m, 1H), **^{13}C**

NMR (126 MHz, DMSO-*d6*); δ 198.3, 152.9, 148.0, 135.6, 135.3, 123.5, HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_6H_6N_2S$ 139.0252; found: 139.0256.

1-Naphthalenecarbothioamide (2r)

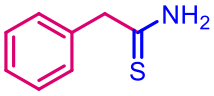
Yellow Crystalline solid; yield 90%; m.p. 198-199 °C; **^{1}H NMR** (500 MHz, DMSO-d_6); δ 10.24 (s, 1H), 9.77 (s, 1H), 8.14 (d, 1H), 7.97-7.92 (m, 2H), 7.59-7.44 (m, 4H), **^{13}C NMR** (126 MHz, DMSO-d_6); δ 202.9, 142.0, 133.4, 128.8, 128.6, 128.5, 126.9, 126.6, 125.5, 125.5, 123.6, HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{11}H_7N_1S_1$ 186.0299; found: 186.02913.

Thioacetamide (2s)



Yellow Crystalline solid; yield 90%; m.p. 197-198 °C; **^{1}H NMR**: (500 MHz, DMSO-d_6); δ 9.29 (s, 1H) 9.17 (s, 1H), **^{13}C NMR** (126 MHz, DMSO-d_6); δ 204.5, 32.9, HRMS (ESI) m/z: [M+H] + calculated for $C_7H_7N_1S_1$ 76.0143; found: 76.0147

Benzeneethanethioamide (2t)



Yellow Crystalline solid; yield 90%; m.p. 106-107 °C; **^{1}H NMR** (500 MHz, DMSO-d_6); δ 4.12 (s, 2H), 7.43-7.41 (m, 3H), 7.37-7.31 (d, 2H), 7.59-7.58 (m, 2H) 7.30-7.28 (m, 2H), **^{13}C NMR** (126 MHz, DMSO-d_6); δ 207.5, 134.8, 133.4, 129.4, 129.3, 129.3, 128.6, 52.0, HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_8H_9N_1S_1$ 152.0456; found: 152.0450.

4.7 Spectral data of a few products

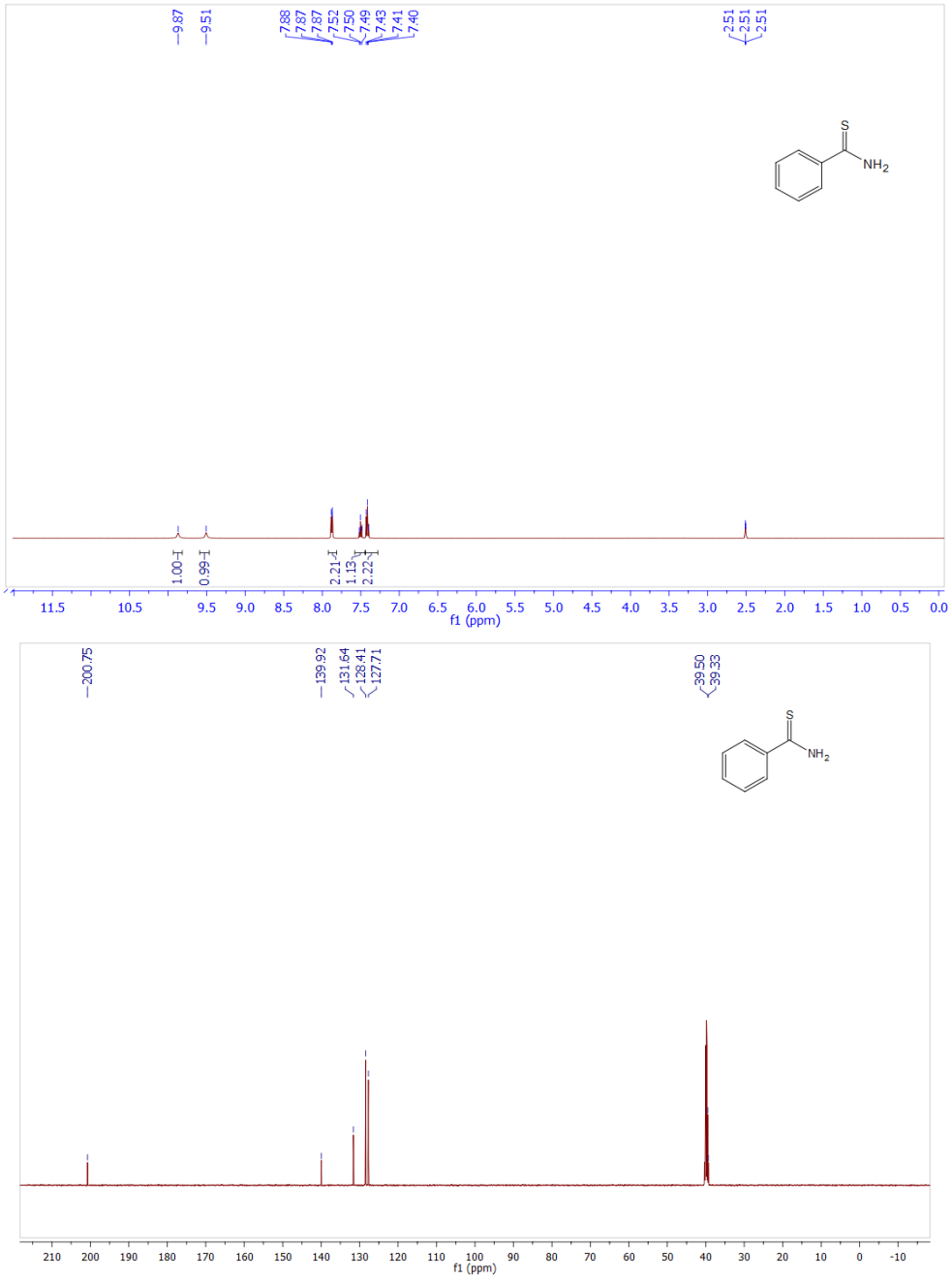


Figure 4.5 ^{1}H & ^{13}C NMR of product **2a**

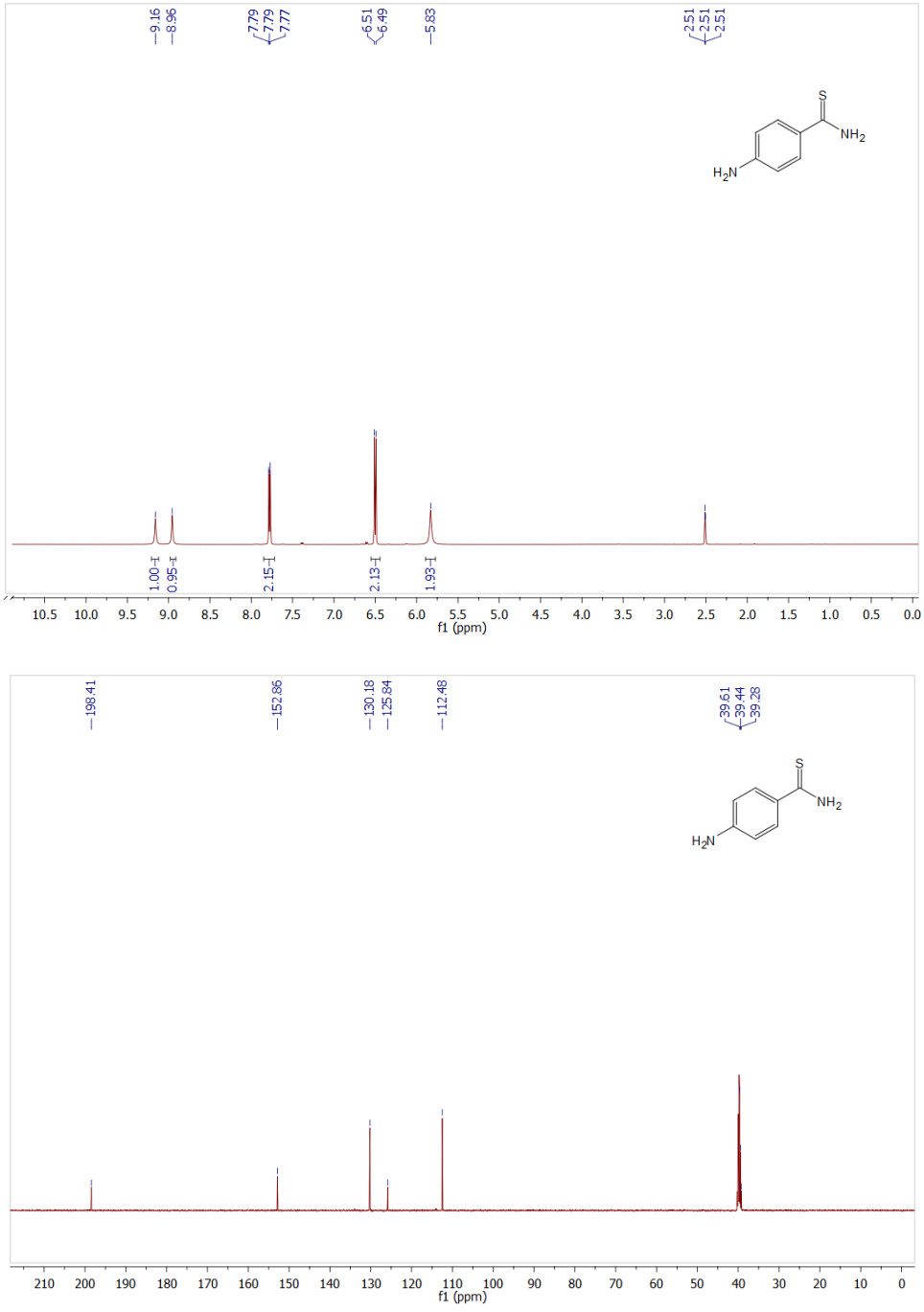


Figure 4.6 ^{1}H & ^{13}C NMR of product **2c**

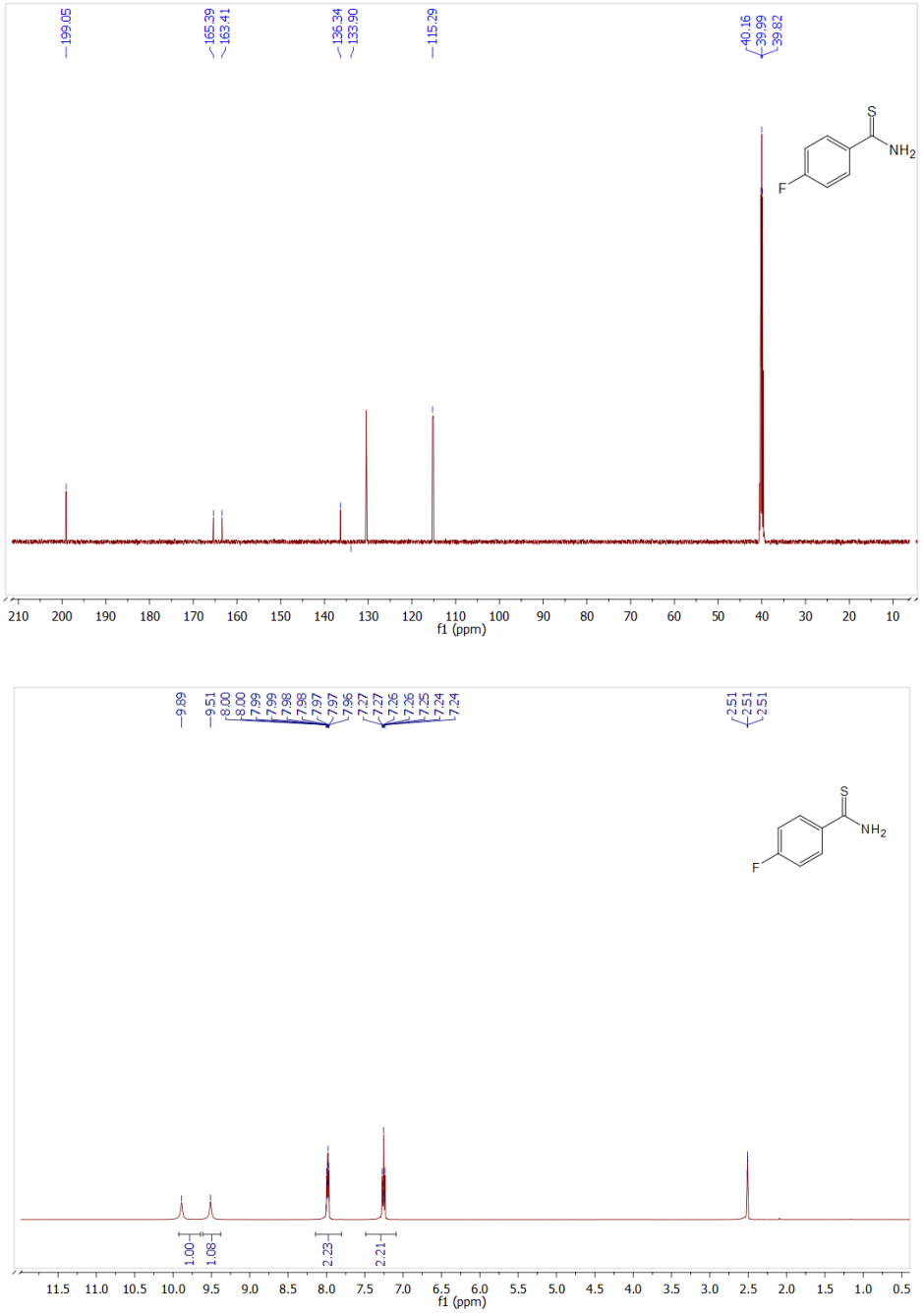


Figure 4.7 ^{1}H & ^{13}C NMR of product **2j**

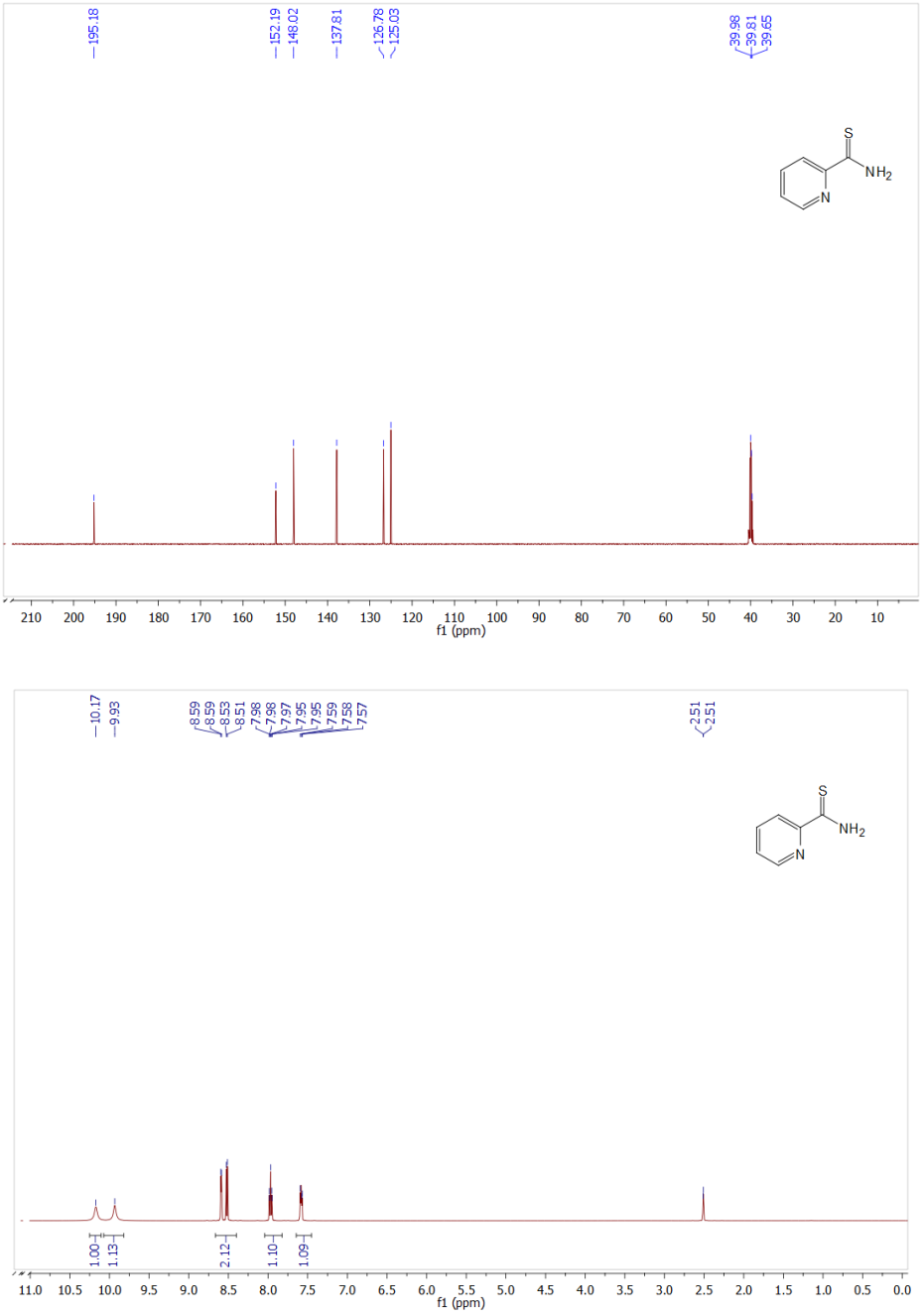


Figure 4.8 ^{1}H & ^{13}C NMR of product **2k**

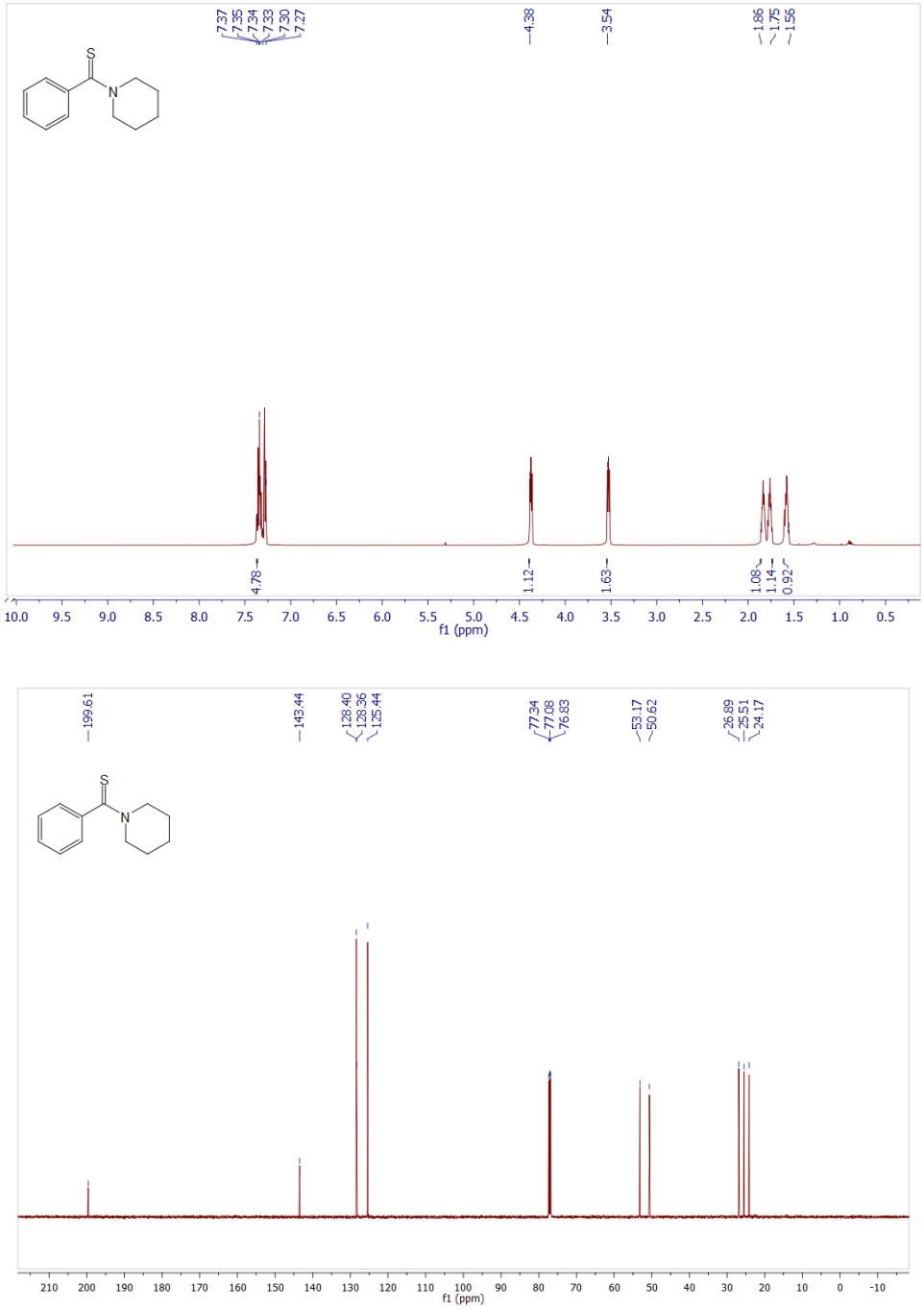


Figure 4.9 ^{1}H & ^{13}C NMR of product **3i**

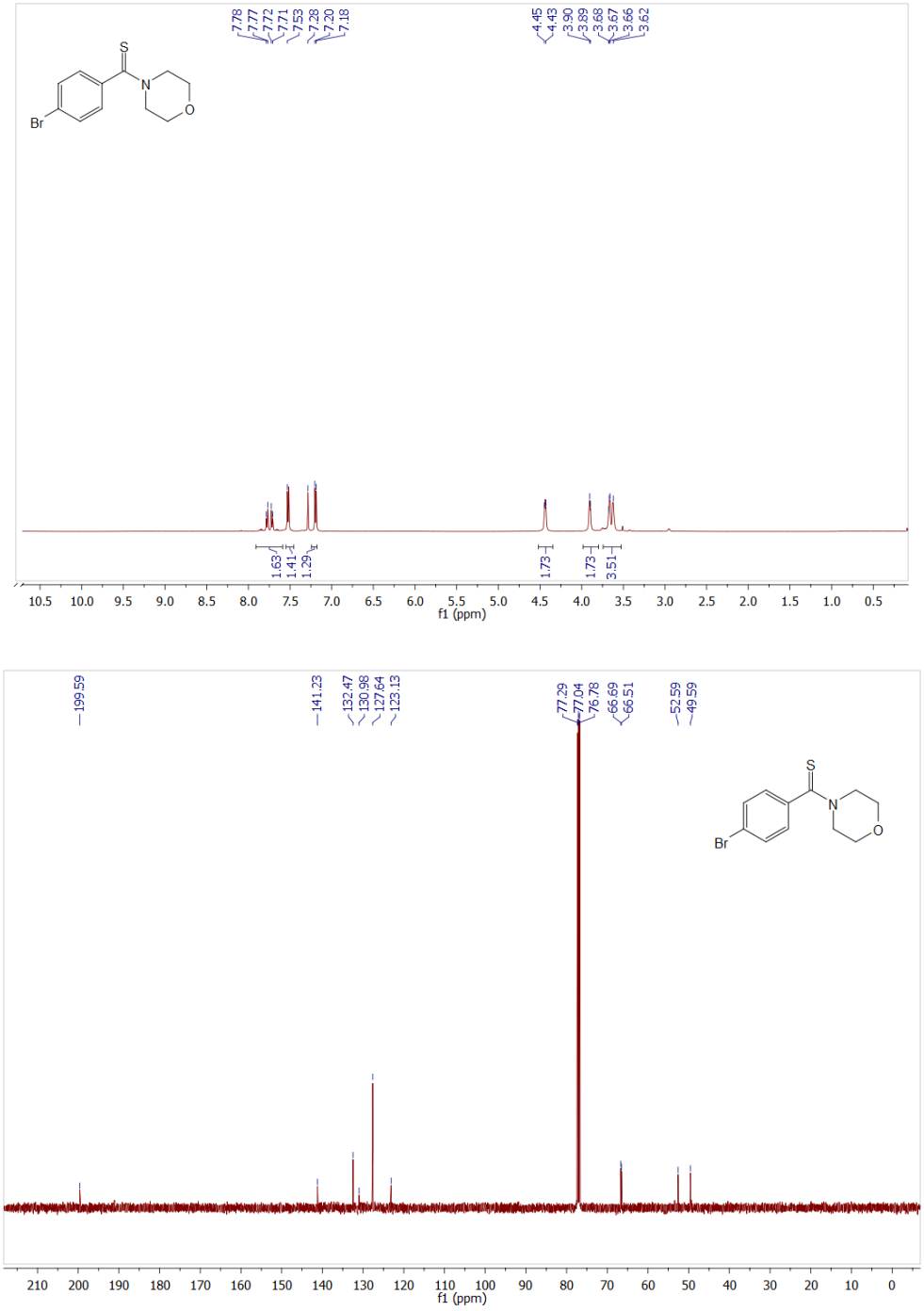


Figure 4.10 ^{1}H & ^{13}C NMR of product **3d**

4.8 Reference

[1] V. Polshettiwar, M. P. Kaushik, "Recent Advances in Thionating Reagents for the Synthesis of Organosulfur Compounds," *Journal of Sulfur Chemistry*, **27** *(*2006) 353-386.

[2] T. S. Jagodziński, "Thioamides as Useful Synthons in the Synthesis of Heterocycles," *Chemical Reviewers*, **103** (2003) 197-228.

[3] P. Wipf, S. A. Venkatraman, "New Thiazole Synthesis by Cyclocondensation of Thioamides and Alkynyl (Aryl) Iodonium Reagents," *The Journal of Organic Chemistry*, **61** (1996) 8004-8005.

[4] D. Kumar, N. M. Kumar, K. H. Chang, R. Gupta, K. Shah, "Synthesis and In-Vitro Anticancer Activity of 3, 5-Bis (Indolyl)-1, 2, 4-Thiadiazoles," *Bioorganic and Medicinal Chemistry Letters*, **21** (2011) 5897-5900.

[5] L. M. T. Frija, A. J. L. Pombeiro, M. N. Kopylovich, "Building 1,2,4-Thiadiazole: Ten Years of Progress" *European Journal of Organic Chemistry*, **19** (2017) 2670-2682.

[6] O. A. Attanasi, S. Berretta, L. D. Crescentini, G. Favi, P. Filippone, G. Giorgi, S. Lillini, F. Mantellini, "Unexpected Regioselectivity in the Reaction between Cycloalkenyl-1-Diazenes and Thioamides: Useful Entry to Fused Cycloalkyl-Thiazoline and Cycloalkyl-Thiazoline–Pyrazole Systems," *Tetrahedron Letters*, **48** (2007) 2449-2451.

[7] A. S. Gurjar, V. Andrisano, A. D. Simone, V. S. Velingkar, "Design, Synthesis, in Silico and in Vitro Screening of 1, 2, 4-Thiadiazole Analogues as Non-Peptide Inhibitors of Beta-Secretase," *Bioorganic Chemistry*, **57** (2014) 90-98.

[8] A. S. Mayhoub, L. Marler, T. P. Kondratyuk, E. J. Park, J. M. Pezzuto, M. Cushman, "Optimizing Thiadiazole Analogues of Resveratrol versus Three Chemopreventive Targets," *Bioorganic and Medicinal Chemistry*, **20** (2012) 510-520.

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

[10] T. Lincke, S. Behnken, K. Ishida, M. Roth, C. Hertweck, "Closthioamide: An Unprecedented Polythioamide Antibiotic from the Strictly Anaerobic Bacterium *Clostridium cellulolyticum*," *Angewandte Chemie,* **122** (2010) 2055-2057.

[11] J. Stachowicz, E. K. Kułak, C. Łukaszuk, A. Niewiadomy, "Relationship between Antifungal Activity against Candida Albicans and Electron Parameters of Selected N-Heterocyclic Thioamides," *Indian Journal of Pharmaceutical Science,* **76** (2014) 287.

[12] F. Wang, R. Langley, G. Gulten, L. G. Dover, G. S. Besra, W. R. Jacobs, J. C. Sacchettini, "Mechanism of Thioamide Drug Action against Tuberculosis and Leprosy," *The Journal of Experimental Medicine,* **204** (2007) 73-78.

[13] Y. A. Tayade, A. D. Jangale, D. S. Dalal, "Simple and Highly Efficient Synthesis of Thioamide Derivatives Using β-Cyclodextrin as Supramolecular Catalyst in Water," *ChemistrySelect, **3*** (2018) 8895-8900.

[14] T. Ozturk, E. Ertas, O. Mert, "Use of Lawesson's Reagent in Organic Syntheses," *Chemical Reviwers,* **107** (2007) 5210-5278.

[15] M. Jesberger, T. P. Davis, L. Barner, "Applications of Lawesson's Reagent in Organic and Organometallic Syntheses," *Synthesis,* **13** (2003) 1929-1958.

[16] Z. Kaleta, B. T. Makowski, T. Soós, R. Dembinski, "Thionation Using Fluorous Lawesson's Reagent," *Organic Letters,* **8** (2006) 1625-1628.

[17] T. J. Curphey, "Thionation with the Reagent Combination of Phosphorus Pentasulfide and Hexamethyldisiloxane," *The Journal of Organic Chemistry,* **67** (2002) 6461-6473.

[18] A. B. Charette, M. Grenon, "Mild Method for the Conversion of Amides to Thioamides," *The Journal of Organic Chemistry,* **68** (2003) 5792-5794.

[19] M. Bagley, K. Chapaneri, C. Glover, E. Merritt, "Simple Microwave-Assisted Method for the Synthesis of Primary Thioamides from Nitriles," *Synlett,* **14** (2004) 2615-2617.

[20] D. C. Smith, S. W. Lee, P. L. Fuchs, "Conversion of Amides and Lactams to Thioamides and Thiolactams Using Hexamethyldisilathiane," *The Journal of Organic Chemistry,* **59** (1994) 348-354.

[21] S. Sharma, D. Singh, S. Kumar, R. Jamra, N. Banyal, C. C. Malakar, V. Singh, "An Efficient Metal-Free and Catalyst-Free C–S/C–O Bond-Formation Strategy: Synthesis of Pyrazole-Conjugated Thioamides and Amides," *Beilstein Journal of Organic Chemistry,* **19** (2023) 231-244.

[22] U. Pathak, L. K. Pandey, R. Tank, "Expeditious Microwave-Assisted Thionation with the System $PSCl_3/H_2$ O/Et_3N under Solvent-Free Condition" *The Journal of Organic Chemistry*, **73** (2008) 2890-2893.

[23] X. Wang, M. Ji, S. Lim, H.Y. Jang, "Thiol as a Synthon for Preparing Thiocarbonyl: Aerobic Oxidation of Thiols for the Synthesis of Thioamides," *The Journal of Organic Chemistry,* **79** (2014) 7256-7260.

[24] T. B. Nguyen, L. Ermolenko, A. A. Mourabit, "Efficient and Selective Multicomponent Oxidative Coupling of Two Different Aliphatic Primary Amines into Thioamides by Elemental Sulfur," *Organic Letters*, **14** (2012) 4274-4277.

[25] J. Liu, S. Zhao, X. Yan, Y. Zhang, S. Zhao, K. Zhuo, Y. Yue, "Elemental-Sulfur-Promoted C(Sp^3)−H Activation of Methyl Heteroarenes Leading to Thioamides," *Asian Journal of Organic Chemistry*, **6** (2017) 1764-1768.

[26] O. I. Zbruyev, N. Stiasni, C. O. Kappe, "Preparation of Thioamide Building Blocks via Microwave-Promoted Three-Component Kindler Reactions," *Journal of Combinatorial Chemistry*, **5** (2003) 145-148.

[27] K. Mahammed, V. Jayashankara, N. P. Rai, K. M. Raju, P. Arunachalam, A Mild and Versatile Synthesis of Thioamides" *Synlett*, **14** (2009) 2338-2340.

[28] R. Liboska, D. Zyka, M. Bobek, "Synthesis of Primary Thioamides from Nitriles and Hydrogen Sulfide Catalyzed by Anion-Exchange Resin," *Synthesis*, **12** (2002) 1649-1651.

[29] F. M. Moghaddam, L. Hojabri, M. Dohendou, "Microwave-Assisted Conversion of Nitriles to Thioamides in Solvent-Free Condition," *Synthetic Communications,* **33** (2003) 4279-4284.

[30] S. D. Fazylov, O. A. Nurkenov, Z. S. Akhmetkarimova, D. R Zhienbaeva, "Synthesis of N-Substituted Thioamides of Benzoic Acids under Microwave Activation," *Russian Journal of General Chemistry*, **82** (2012) 781-782.

[31] J. H. Hillhouse, I. A. Blair, L. Field, "Thiono compounds, oxidation of thioamides in relation to adverse biological effects," *Phosphorous and Sulfur and the Related Elements,* **26** (1986) 169-184.

[32] R. S. Varma, D. Kumar, "Microwave-accelerated solvent-free synthesis of thioketones, thiolactones, thioamides, thionoesters, and thioflavonoids," *Organic Letters,* **1** (1999) 697-700.

[33] M. D. Goodwin, M. Q. Costa, J. R. Robinson, C. M. Kotyk, "Mechanochemical synthesis of thiolactams and other thioamides using Lawesson's reagent," *Results in Chemistry,* **4** (2022) 100528-10053.

[34] K. Wu, Y. Ling, A. Ding, L. Jin, N. Sun, B. Hu, Z. Shen, X. Hu, "A Chromatography-Free and Aqueous Waste-Free Process for Thioamide Preparation with Lawesson's Reagent. *Beilstein*," *The Journal of Organic Chemistry,* **17** (2021) 805-812.

[35] Q. Zhang, L. Soulère, Y. Queneau, "Towards More Practical Methods for the Chemical Synthesis of Thioamides Using Sulfuration Agents: A Decade Update," *Molecules,* **28** (2023) 3527.

[36] H. Jin, X. Chen, C. Qian, X. Ge, S. Zhou, "Transition-Metal-Free, General Construction of Thioamides from Chlorohydrocarbon, Amide, and Elemental Sulfur," *European Journal of Organic Chemistry,* **23** (2021) 3403-3406.

[37] K. Bayram, B. Kiskan, Y. Yagci, "Synthesis of Thioamide Containing Polybenzoxazines by the Willgerodt–Kindler Reaction," *Polymer Chemistry,* **12** (2021) 534–544.

[38] V. Singh, K. Rajput, A. Mishra, S. Singh, V. Srivastava, "A Green Approach for the Synthesis of 2-Oxo-1,2,3,4-Tetrahydropyrimidines through Oxidative Functionalization of Methyl Arenes/Benzyl Derivatives via in Situ Generated Urea," *Research on Chemical Intermediate,* **49** (2023) 2969-2987.

[39] V. Singh, K. Rajput, A. Mishra, S. Singh, V. Srivastava, "Microwave-Assisted Chemoselective Transamidation of Secondary Amides by Selective N–C (O) Bond Cleavage under Catalyst, Additive and Solvent-Free Conditions," *Chemical Communications,* **59** (2023) 14009-14012.

[40] W. Przychodzeń, "Mechanism of the Reaction of Lawesson's Reagent with *N* -Alkylhydroxamic Acids," *European Journal of Organic Chemistry,* **2005** (*2005*) 2002-2014.

[41] K. Wu, Y. Ling, A. Ding, L. Jin, N. Sun, B. Hu, Z. Shen, X. Hu, "A Chromatography-Free and Aqueous Waste-Free Process for Thioamide Preparation with Lawesson's Reagent. *Beilstein*," *The Journal of Organic Chemistry,* **17** (2021) 805-812.

[42] J. Zakrzewski, M. Krawczyk, "Reactions of Nitroxides with Sulfur-Containing Compounds, Part IV: Synthesis of Novel Nitroxide (Thio)Ureas," *Heteroatom Chemistry: An International Journal of Main Group Elements,* **17** (2006) 393-401.

[43] H. Khatoon, E. Abdulmalek, "A Focused Review of Synthetic Applications of Lawesson's Reagent in Organic Synthesis," *Molecules,* **26** (2021) 6937.