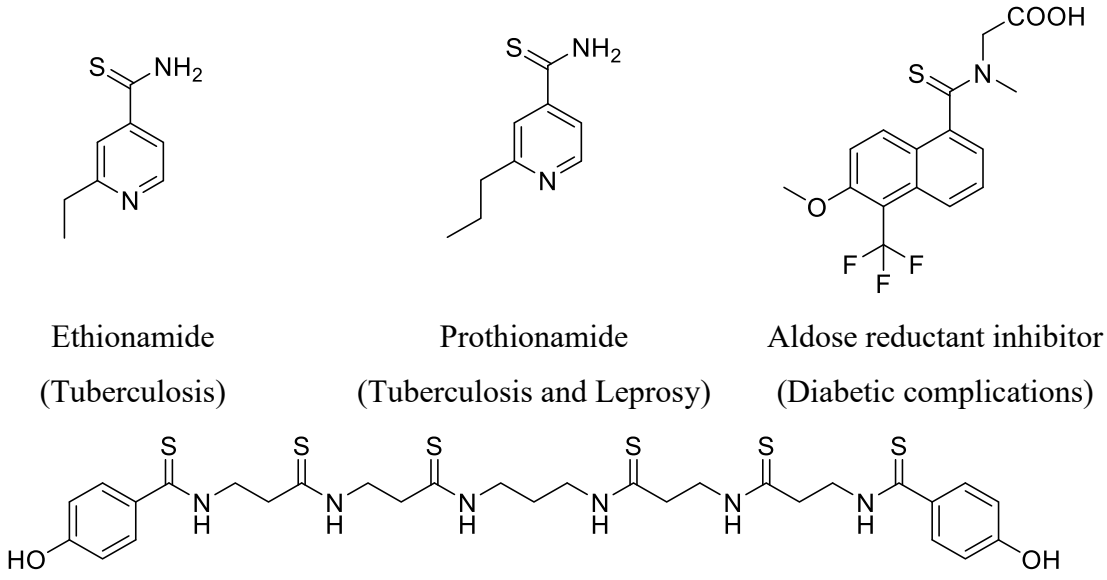
Chapter III

Humic acid catalyzed solvent-free green protocol for synthesis of thioamide

III.A. Introduction

Thioamides were first introduced in the year 1815 by Gay-Lussak and later by Berzelius in 1843 by conversion of amides to its thio analogs is the basis of thioamide formations. Thioamide derivatives have been explored from long time in synthesis of various important thio-heterocyclic compounds like thiazoles[1-3], tetrazoles[1], thiazolins[4], thiazolinones[4]. These bioactive thio heterocycles have huge range of applicability in the field of various important medicinal and pharmateutical applications. P-glycoprotein, a modulators of the ATP binding cassette transporters[5]; closthioamide, a polythioamide antibiotics[6]; *N*-cyclohexylethyl-ETASV, an inhibitor of the PSD-95-NMDA receptor interaction[7]; antithyroid drugs[8]; these examples amplify the application of bioactive thio-compounds in medicinal and ptherapeutic field and a few such derivatives are presented in Figure III.1 as well.



Ethionamide (Tuberculosis)

Prothionamide (Tuberculosis and Leprosy)

Aldose reductant inhibitor (Diabetic complications)

Closthioamide (Polythioamide antibiotic)

Figure III.1. Few Biologically active compounds having thioamide moiety.

Thioamide derivatives are also widely used as grease additives, vulcanization agents, plastic pigments, petroleum products[9], as ligands for estrogen receptors[10], as aldose reductase inhibitors[11], as fungistatic molecules[12] etc.

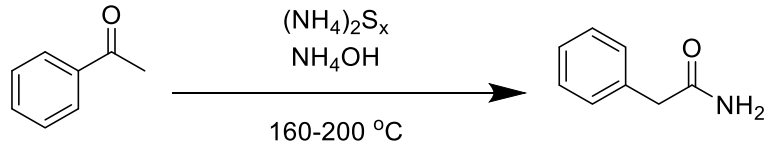
III.B. Background and Objectives

For synthesis of thioamides, various methods have been developed previously. Precursors like amines, nitriles, amides, oximes, carboxylic acids, carbonyls, and thiols have been employed for such synthesis. The most conventional method for synthesis of thioamide is use of Lawesson's reagent[13]. Moreover, thioamide have been synthesized by reaction of formamide

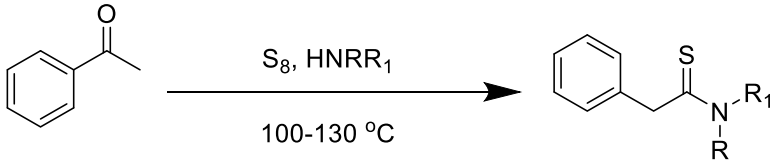
with aldehyde in sodium sulphide and presence of water[14], copper (II) catalyzed oxidation of thiols in presence of compounds like 1,5,7-triazabicyclo[4.4.0]dec-5-ene[15] and oxidative coupling of primary amine with sulphur[16]. Owing to use of expensive metal catalysts, noxious solvents, harsh reaction condition, longer reaction time etc. these protocols need advancement from the green chemistry standpoint to make the process environmentally sustainable.

III.B.1. Specialized methods for synthesis of thioamides

In 1887 Conrad Willgerodt first described formation of amides from ketones by treating it with ammonium hydroxide, and ammonium polysulfide at 160-200 °C temperature[17] (Scheme III.1). In 1923 Karl Kindler modified the scheme using secondary amines in presence of sulfur at 100-130 °C to yield thioamides successfully[18] (Scheme III.2).

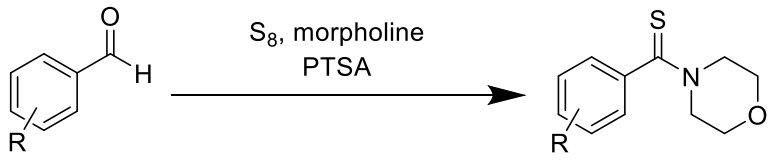


Scheme III.1. Synthesis of amides by Willgerodt reaction.



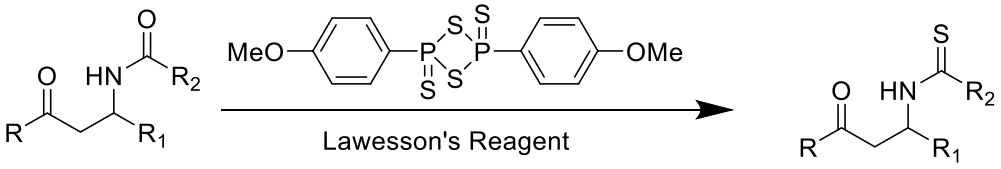
Scheme III.2. Synthesis of thioamides by Kindler modification.

The Willgerodt–Kindler reaction is not widely used nowadays in organic syntheses is due to the disadvantage that this process produces low yield and provides complex reaction mixtures. In late 1970's Kul'ganek *et al.* reported preparation of thioamides using morpholine in PTSA as catalyst[19]. By this reaction aldehyde derivatives could also be converted into thioamides for the first time. Further, dialdehydes like *o-,m-,p-* pthalaldehydes undergo this reaction too (Scheme III.3). The major drawback of this reaction is use of PTSA which is hazardous strong acid.



Scheme III.3. Synthesis of thioamides using PTSA.

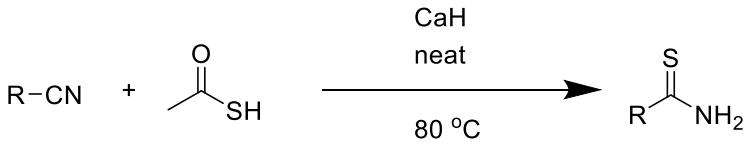
Another notable method is developed by using Lawesson's reagent. Lawesson's reagent was first prepared in 1956 while doing a systematic study of the reactions of arenes with P_4S_{10}[20]. One such example is Nishio et al. investigated the thionation reactions of beta-hydroxy amides which resulted in the formation of unsaturated thioamide[21] (Scheme III.4).



Scheme III.4. Synthesis of thioamide by Lawesson's reagent.

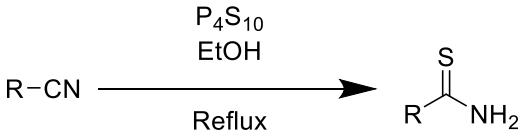
III.B.2. Modern approach towards thioamide synthesis

P. N. Arunachalam *et al.* developed modern method for synthesis of thioamide from aliphatic and aromatic nitriles[22]. Thioacetic acid is used in this reaction with presence of calcium hydride to produce corresponding thioamide in good to excellent yield (Scheme III.5). A major drawback of this reaction is haloaryl nitriles do not undergo this method under given condition. And use of nitrile as precursor always makes the method harmful to handle and limits its scalability.



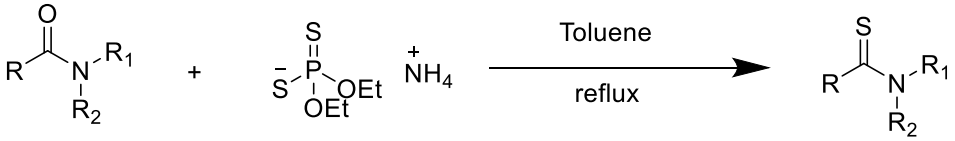
Scheme III.5. Synthesis of thioamide by thioacetic acid and calcium hydride.

Another efficient method of synthesis of thioamide from nitrile is reported by D. Elhamifar *et al.*[23] Aliphatic and aromatic nitriles undergo this reaction with good yield of corresponding product. In this reaction phosphorus pentasulfide is used in ethanol under reflux condition (Scheme III.6). It is a rapid, high yielding process but the drawback lies within nitrile precursor.



Scheme III.6. Synthesis of thioamide using phosphorus pentasulfide

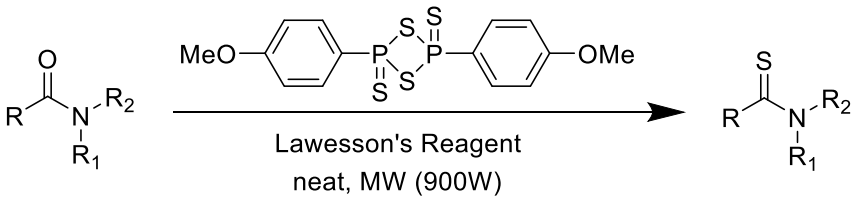
Thionation of amide can be used as another route for synthesis of thioamides and that is reported by L. Malekzadeh *et al.* in 2011. Wide range of aromatic and aliphatic amides are converted into thioamides using ammonium phosphorodithioate[24]. Toluene is used as solvent under reflux condition (Scheme III.7). This reaction can take up to 10 hours in specific cases.



Scheme III.7. Synthesis of thioamide using ammonium phosphorodithioate

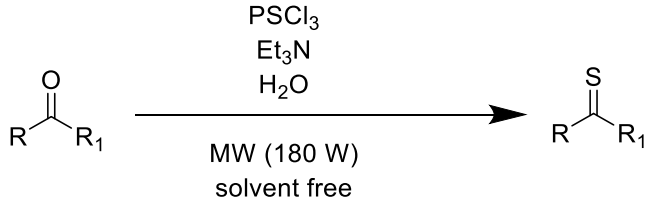
Microwave irradiated method for conversion of amides to thioamides is reported by D. Kumar *et al.* using Lawesson's reagent[25]. The reaction is performed in solvent-free condition in an

open vessel and product obtained in 2-4 minutes (Scheme III.8). Excess of reagent is required for this process annthe method is not very cost effective.



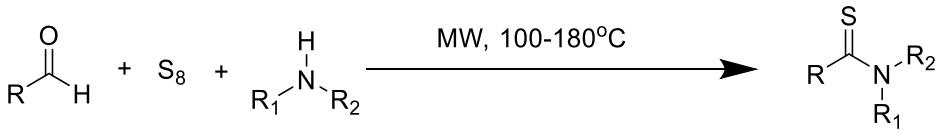
Scheme III.8. Microwave assisted synthesis of thioamide using Lawesson's reagent.

Another microwave assisted method is reported by R. Tank *et al.* from carbonyl compounds. They used $PSCl_3/H_2O/Et_3N$ system for thioamide formation[26]. Along with thioamides this method is also capable of forming other products like thiolactams, thioketones, thioxanthones and thioacridone. The process is reported under solvent-free condition at 70-100 ºC and completion time is within 6 minutes (Scheme III.9).



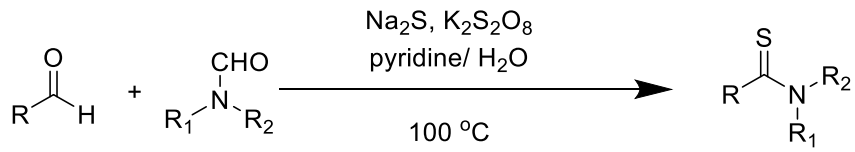
Scheme III.9. Synthesis of thioamide with microwave assistance using $PSCl_3/H_2O/Et_3N$ system.

A microwave assisted three component thioamide synthesis is reported by C. O. Kappe *et al.* in Kindler type reaction[27]. Aldehydes, amines and elemental sulfur were reacted using 1-methyl-2-pyrrolidone as solvent at 110-180 ºC. Good yield of products obtained within 20 minutes (Scheme III.10).



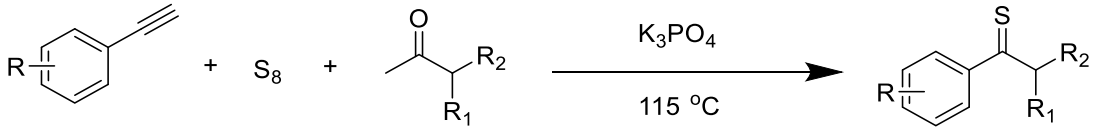
Scheme III.10. Synthesis of thioamide by three component synthesis using microwave irradiation.

In recent time, a very effective synthetic method for thioamide synthesis is reported by X. Jiang *et al*. from aldehydes[28]. *N*-substituted formamides are reacted with aldehydes using sodium sulphide in water and pyridine medium at 100 ºC to yield corresponding thioamide (Scheme III.11). Modifications of bioactive molecules are also represented in this article. Requirement of up to 24-hour time of completion for the reaction is a limitation of this process.



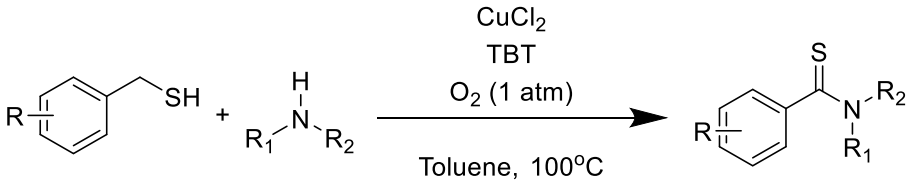
Scheme III.11. Synthesis of thioamide from *N*-substituted formamides using sodium sulphide.

Another recent advancement towards thioamide synthesis is reported by L. Liu *et al.*[29]. Starting with aromatic alkyne the reported transition metal-free cleavage of C-C triple bond in presence of amide and sulfur to yield thioamide (Scheme III.12). Wide substrate scope is reported by the author and the method is suitable for some internal aromatic alkynes and acetamides. Though time requirement of 20 hours is a limitation of the process at 115 °C.



Scheme III.12. Synthesis of thioamide from aromatic alkynes.

A substitute route for synthesis of thioamides from thiols is reported by H.Y. Jang *et al.*[30] Thiols are used as starting material to bypass the use of elemental sulfur in this case. As a catalyst Cu(II) salt is used in presence of tributyltin (TBT) (Scheme III.13). O_2 is supplied in 1 atm pressure during the reaction at 100 °C in toluene medium. Use of metal catalyst, up to 18 hour reaction time and requirement of O_2 during the reaction makes the reaction hazardous and non-economical.



Scheme III.13. Synthesis of thioamides from thiols using Cu(II) salt and tributyltin.

III.B.3. Background of Humic acid in organic synthesis

Now a days, to construct a protocol environmentally sustainable and greener, substitution of these detrimental catalysts and solvents are desirable in drug chemistry and in organic synthesis too. As a greener alternative catalyst, biodegradable high molecular weight materials are getting noteworthy attention due to their ease of handling, low toxicity and easily separable, recoverable also reusable nature in many cases. Among these alternates, humic acid is rarely explored polymer that has potential to manifest extraordinary catalytic activity owing to the presence of functional groups like carboxyl (-COOH) and hydroxyl (=CH-OH) in its structure (Figure III.2).

Humic acid is mostly obtained from the biodegradation of deceased organic materials available as soil, coal, peat, upland streams, dystrophic lakes and well water. From a green standpoint humic acid is non-toxic, inexpensive, easily accessible, environmentally benign, organo catalyst which is reported in very limited articles.

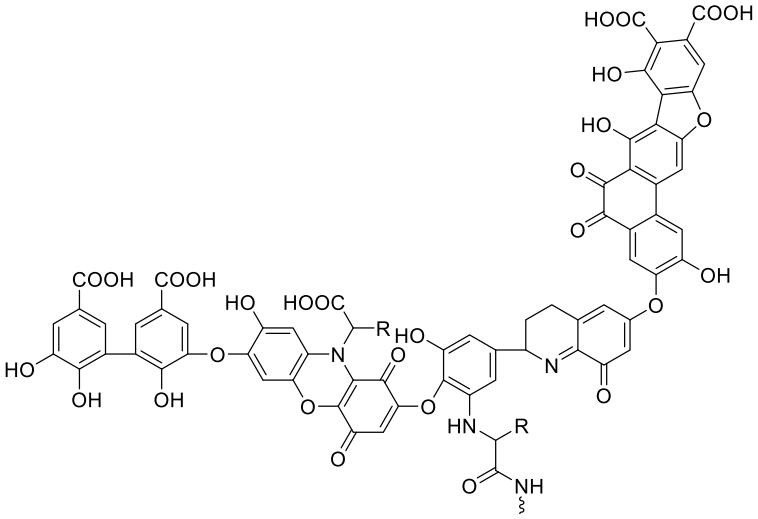
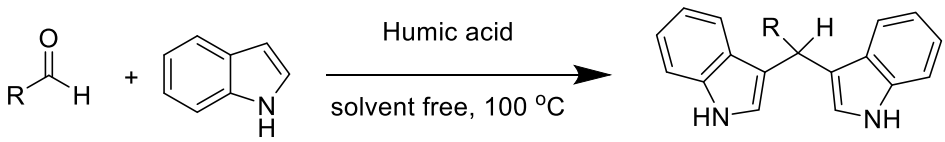


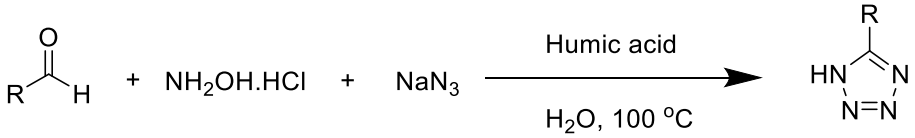
Figure III.2. Structure of Humic acid.

In 2020, P. Ghosh *et al.* reported a facile synthesis of Bis(indolyl)methanes, Bis(pyrazolyl) methanes, Bis-coumarins and Bis-lawsones catalyzed by humic acid in solvent-free condition[31] (Scheme III.14). Some of the major advantages they achieved in this method over other conventional methods are, no hazardous solvents required, toxic metal catalysts-free, no harsh reaction conditions, low catalyst loading, good yield and excellent functional group tolerance.



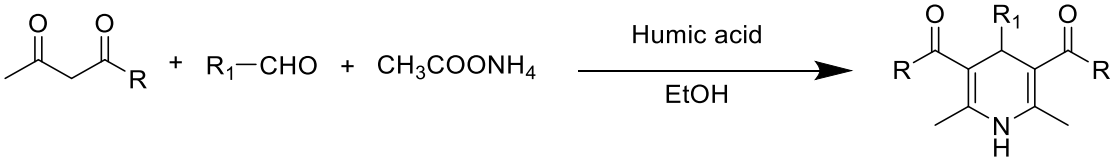
Scheme III.14. Synthesis of some diversified bis(indolyl)methane from aldehydes.

Another application of humic acid as organocatalyst is reported by X. Wang *et al.* in 2020[32]. They synthesized 5-substituted 1*H*-tetrazoles in water using humic acid as catalyst. Aldehydes, hydroxyamine hydrochloride and sodium azide are used as starting material in water (Scheme III.15).



Scheme III.15. Humic acid catalyzed one-pot three-component synthesis of 5-substituted 1*H*-tetrazoles.

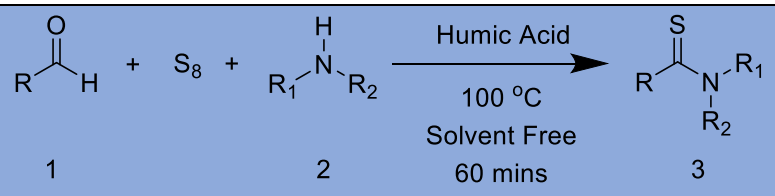
In 2017, W. Yongqiu *et al.* reported Synthesis of 1,4-Dihydropyridine compounds catalyzed by humic acid[33]. Synthesis of 1,4-dihydropyridine compounds is reported through Hantzsch reaction in this article. Aldehydes, ammonium acetate and ethyl acetoacetate or methyl acetoacetate are used as starting material to achieve desired product in this reaction (Scheme III. 16). Various aldehydes and diketones are employed in the process with excellent yield of corresponding product. Ethanol is used as greener solvent for this protocol.



Scheme III.16. Synthesis 1,4-dihydropyridine compounds with humic acid.

III.C. Present work

Here we are reporting an environmentally sustainable, green synthesis of thioamide through MCR of aldehyde, amine and sulfur catalyzed by humic acid in solvent -free condition at 100°C. The key features of this protocol is use of humic acid, a greener, easily recyclable, easily available and almost unexplored catalyst and circumvention of noxious solvents that amplify the scope of the reaction. The proposed protocol also possess tolerance to aromatic as well as aliphatic aldehydes and amines comprising variety electron donating and withdrawing functional groups.



R = Aryl, Heterocyclic, Aliphatic

R_1, R_2 = Aryl, H, Alkyl, Heterocyclic, Alicyclic

Scheme III.17. Synthesis of thioamides from aldehydes and amines.

III.C.1. Result and discussion

To perpetuate the optimum condition for our continuing effort on humic acid catalyzed green synthetic methodology we started with benzaldehyde, pyrrolidine and sulfur as a model reaction. While optimizing we found that time and temperature has significant effect on the reaction. The temperature effect was investigated at ambient, 80 °C and 100 °C (Table III.1). Though at room temperature no yield of desired product was reported (Table III.1, entry 7) but gradually increase in temperature upto 100 °C (Table III.1, entry 9) shows notable increase in the yield. We examined with various solvents and in solvent -free condition, none of the

solvents appear to be advantageous than solvent -free condition. Hence 100 ºC and solvent -free condition is chosen as best for our Humic acid catalyzed reaction condition (Table III.1).

Table III.1. [a]Optimization of time, temperature and solvent for synthesis of thioamide.

Entry	Solvent	Temperature (ºC)	Time (min)	Yield [%][b]
1	Ethanol	Reflux	180	-
2	Methanol	Reflux	180	-
3	Water	Reflux	180	Trace
4	Ethylene glycol	100	180	Trace
5	Solvent -free	100	180	93
6	Solvent -free	80	180	72
7	Solvent -free	RT	180	46
8	Solvent -free	100	120	92
9	**Solvent -free**	**100**	**60**	**91**

The bold signifies most optimized condition.

[a] Reaction of Reaction of Benzaldehyde (1 mmol), pyrolidine (1 mmol) and sulphur (1.25 mmol) in presence of Humic acid catalyst.

[b] Isolated yield

Now, to optimize the amount of sulfur we started with 0.25 mmol (Table III.2, entry 1) of sulfur, where we did not achieve desired yield. Upon increasing the the amount of sulfur to 1.25 mmol (Table III.2, entry 4) and 1.50 mmol (Table III.2, entry 5) respectively the yield of desired thioamide also increased but was almost the same for both the cases. The amount of catalyst loading was also optimized and 15 mg (Table III.2, entry 7) was found to be the best for our scheme (Table III.2).

Table III.2. [a]Optimization of amount of catalyst and amount of sulfur for synthesis of thioamide.

Entry	Catalyst Loading (mg)	Sulfur (mmol)	Yield [%][b]
1	50	0.25	52
2	50	0.50	68
3	50	1.00	83
4	50	1.25	91
5	50	1.50	93
6	25	1.25	92
7	**15**	**1.25**	**91**

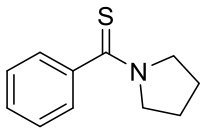
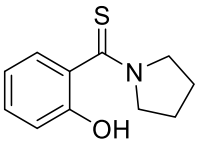
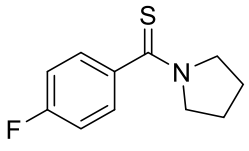
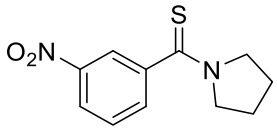
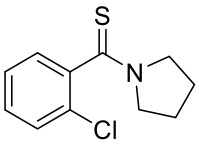
The bold signifies most optimized condition.

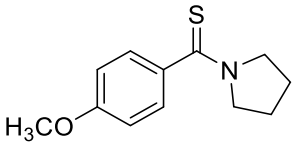
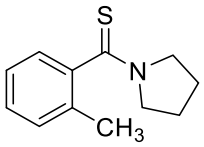
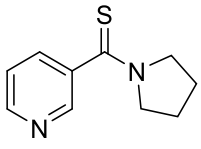
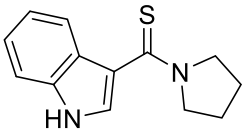
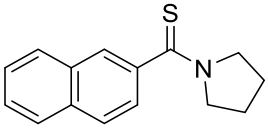
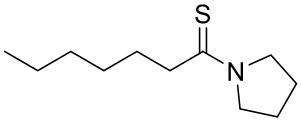
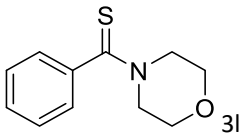
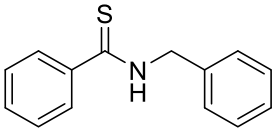
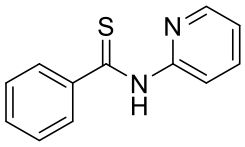
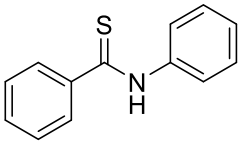
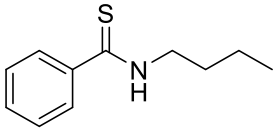
[a] Reaction of Reaction of Benzaldehyde (1 mmol), pyrolidine (1 mmol) and sulphur (1.25 mmol) in presence of humic acid catalyst.

[b] Isolated yield

Afterwards, the efficiency of the reagents was investigated under optimized reaction condition for condensation of pyrrolidine with broad range of aldehydes to produce the desired products. The reaction was successful for phenyl group in benzaldehyde (Table III.3, entry 3a-3k) bearing electron withdrawing substituents like nitro, chloro and fluoro groups (Table III.3, entry 3c, 3d, 3e) as well as electron donating groups such as methoxy, hydroxy and methyl groups (Table III.3, entry 3b, 3f, 3g). Aliphatic and heterocyclic aldehydes (Table III.3, entry 3h, 3i, 3k) also produce moderate to good yield under optimized condition. The applicability of the protocol was also examined over vast range of amines having pyridine, benzyl, alicyclic, aromatic motif (Table III.3, entry 3l-3p) which successfully produced respective desired thioamide in good yield (Table III.3).

Table III.3. [a]Synthesis of some diversified thioamides derivatives under solvent-free condition catalyzed by Humic acid.

Entry	Product	Yield[%][b]
1	 3a	91
2	 3b	82
3	 3c	90
4	 3d	83
5	 3e	76

6	 3f	90
7	 3g	82
8	 3h	76
9	 3i	73
10	 3j	78
11	 3k	80
12	 3l	86
13	 3m	67
14	 3n	64
15	 3o	60
16	 3p	78

[a]Reaction condition: Aldehyde (1 mmol), pyrrolidine (1 mmol) and sulphur (1. 25 mmol) in presence of 15 mg humic acid in solvent -free condition at 100 °C for 60 min;
[b]Isolated yield of product by column chromatography.

III.C.2. Catalyst recovery

The catalyst recovery and reusability were investigated by four cycles counting the use of fresh catalyst for the preparation of phenyl(pyrrolidin-1-yl)methanethione (Table III.3, entry 3a) by the reaction of Aldehyde (1 mmol), pyrrolidine (1 mmol) and sulphur (1. 25 mmol) in presence of 15 mg humic acid in solvent -free condition at 100 °C for 60 min. After the completion of the 1st run, ethyl acetate was added to the reaction mixture (5 mL). The catalyst was easily recovered from the reaction mixture by simple filtration. It was washed with ethyl acetate (3×5 mL) several times and then dried before being used for the next run. After every cycle, the catalyst was almost quantitatively recovered with slight loss in amount up to fourth run. But on fifth cycle, notable decrease in yield and recovery of catalyst was observed.

III.D. Conclusion

In conclusion, we have established a, environmentally benign, upfront and simplistic strategy for the synthesis of functionalized thioamide derivatives under solvent--free condition using humic acid without using any metal catalyst. Absence of any solvent further improves the advantage of the protocol. Catalyst can be recovered by simple filtration which makes these protocols more attractive in the field of green organic synthesis. Replacement of toxic and expensive metal catalyst by environment friendly and inexpensive humic acid is the uniqueness of this protocol which may be helpful in the medicinal as well as industrial chemistry.

III.E. Experimental

III.E.1. General Information

^{1}H NMR, ^{19}F NMR and ^{13}C NMR were recorded using 400 MHz, 376 MHz and 100 MHz Bruker Avance FT-NMR Spectrometer using TMS as internal standard. Splitting patterns of protons were described as s (singlet), d (doublet), t (triplet), br (broad), q (quartet) and m (multiplet).

III.E.2. General procedure

In our general procedure, a mixture of aldehyde (1 mmol), amine (1 mmol) and sulphur (1.25 mmol) in presence of 15 mg humic acid in solvent -free condition at 100°C for 60 min in a 50 mL round-bottom flask using a magnetic stirring bar under open air for 30-60 min and the progress of the reaction was monitored on the TLC. After completion of the reaction the reaction mixture was cooled, then the solution was poured into 100 mL water and extract with ethyl acetate, washed several times with water. The combined organic mixture was dried over

anhydrous Na_2SO_4, concentrated and the residue was purified by column chromatography on silica gel 60–120 mesh using petroleum ether/ethyl acetate as eluent to afford the pure product. All compounds were analyzed by NMR techniques.

III.E.3. Spectroscopy data

1. Phenyl(pyrrolidin-1-yl)methanethione: (Table III.3, entry 3a)

Yellow solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.91-2.11 (m, 4H), 3.46 (t, *J* = 6.6 Hz, 2H), 3.98 (t, *J* = 6.6 Hz, 2H), 7.27-7.40 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 24.67, 26.49, 52.42, 53.81, 125.63, 128.30, 128.72, 143.98, 197.22.

2. (4-fluorophenyl)(pyrrolidin-1-yl)methanethione: (Table III.3, entry 3c)

Brown solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.90 (s, 2H), 2.00 (d, *J*= 4.8 Hz, 2H), 3.40 (d, *J* = 3.6 Hz, 2H), 3.87 (s, 2H), 6.95-7.31 (m, 4H).

^{19}F NMR (376 MHz, DMSO-d_6) δ (ppm): -112.20 (s, 1F).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 24.72, 26.60, 53.74, 54.03, 115.16, 115.38, 127.95, 128.04. 140.12, 140.15, 161.50, 163.98, 195.95.

3. (3-nitrophenyl)(pyrrolidin-1-yl)methanethione: (Table III.3, entry 3d)

Brown solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.00-2.19 (m, 1H), 3.58 (t, *J* = 6.6 Hz, 2H), 3.89 (t, *J* = 6.6 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 7.0 Hz, 1H), 8.09-8.14 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 23.15, 26.31, 52.97, 53.87, 121.64, 122.70, 127.56, 130.56, 145.35, 146.78, 193.26.

4. (4-methoxyphenyl)(pyrrolidin-1-yl)methanethione: (Table III.3, entry 3f)

Yellow solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.80-1.95 (m, 4H), 3.40 (t, *J* = 4.8 Hz, 2H), 3.67 (s, 3H), 3.81 (t, *J* = 6.0 Hz, 2H), 6.71-6.74 (m, 2H), 7.23-7.26 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 24.73, 26.61, 53.83, 54.11, 55.47, 55.60, 113.05, 113.41, 113.72, 127.50, 127.80, 128.08, 132.09, 136.48, 160.06, 196.82.

5. (pyrrolidin-1-yl)(o-tolyl)methanethione: (Table III.3, entry 3h)

Brown liquid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.89-2.03 (m, 2H), 2.18 (s, 3H), 3.26 (t, *J* =5.8 Hz, 1H), 3.28 (t, *J* = 6.0 Hz, 1H), 7.04-7.27 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm):17.98, 25.45, 25.87, 51.36, 52.09, 122.58, 126.83, 127.99, 131.56, 143.95, 197.87.

6. (1*H*-indol-3-yl)(pyrrolidin-1-yl)methanethione: (Table III.3, entry 3i)

Brown solid;

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.78-1.95 (m, 4H), 3.71 (t, *J* = 5.8 Hz, 2H), 3.83 (t, *J* = 6.6 Hz, 2H), 7.01-7.14 (m, 2H), 7.47 (d, *J* = 5.8 Hz, 1H), 7.67 (d, *J* = 5.7 Hz, 1H), 7.93 (d, *J* = 5.8 Hz, 1H), 10.98 (s, 1H);

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 23.75, 27.45, 52.93, 113.85, 117.68, 121.08, 121.78, 123.75, 124.72, 127.44, 135.79, 191.07.

7. (naphthalen-3-yl)(pyrrolidin-1-yl)methanethione: (Table III.3, entry 3j)

Yellow solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.72-2.01 (m, 4H), 3.48 (t, *J* = 6.0 Hz, 2H), 3.89 (t, *J* = 6.0 Hz, 2H), 7.35-7.41 (m, 5H), 7.69 (t, *J* = 5.9 Hz, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 22.88, 25.87, 53.24, 53.67, 121.66, 123.32, 125.96, 126.34, 126.93, 128.65, 128.91, 131.36, 135.37, 140.46, 198.01.

8. Morpholino(phenyl)methanethione:[34] (Table III.3, entry 3l)

Yellow solid;

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.64-3.63 (m, 4H), 3.90 (t, *J* = 4.6 Hz, 2H), 4.46 (t, *J* = 4.8 Hz, 2H), 7.38-7.27 (m, 5H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 49.17, 52.20, 65.65, 65.94, 125.78, 128.22, 128.47, 142.35, 161.83, 198.66.

9. *N*-benzylbenzothioamide: (Table III.3, entry 3m)

Brown liquid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.79 (s, 2H), 7.13-7.37 (m, 8H), 7.59 (d, *J* = 5.4 Hz, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 48.47, 124.87, 126.99, 127.22, 128.13, 129.46, 131.78, 134.62, 138.37, 197.93.

10. *N*-butylbenzothioamide: (Table III.3, entry 3p)

Yellow solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.03 (t, 3H), 1.36 (q, 2H), 1.57-1.65 (m, 2H), 3.61-3.77 (m, 2H), 7.25-7.63 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm):11.86, 20.35, 27.76, 45.07, 124.29, 126.85, 130.12, 142.49, 197.91

III.E.4. Scanned copies of ^{1}H and ^{13}C NMR of the derivatives

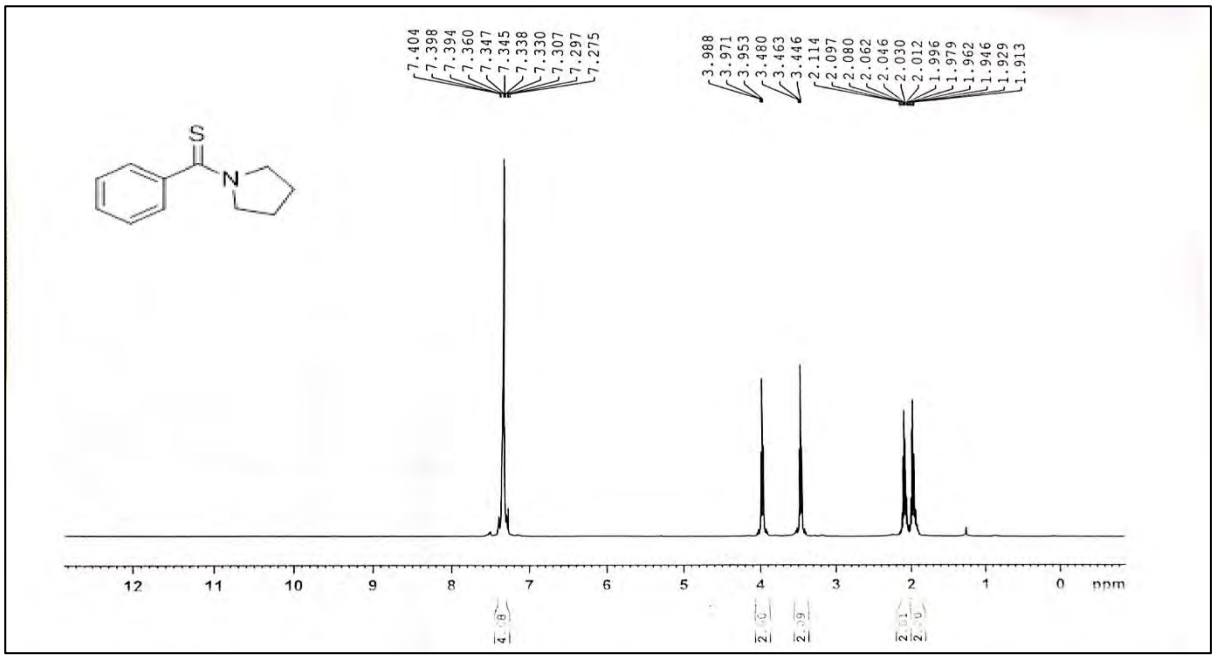


Figure III.3. Scan copy of ^{1}H NMR of Phenyl(pyrrolidin-1-yl)methanethione.

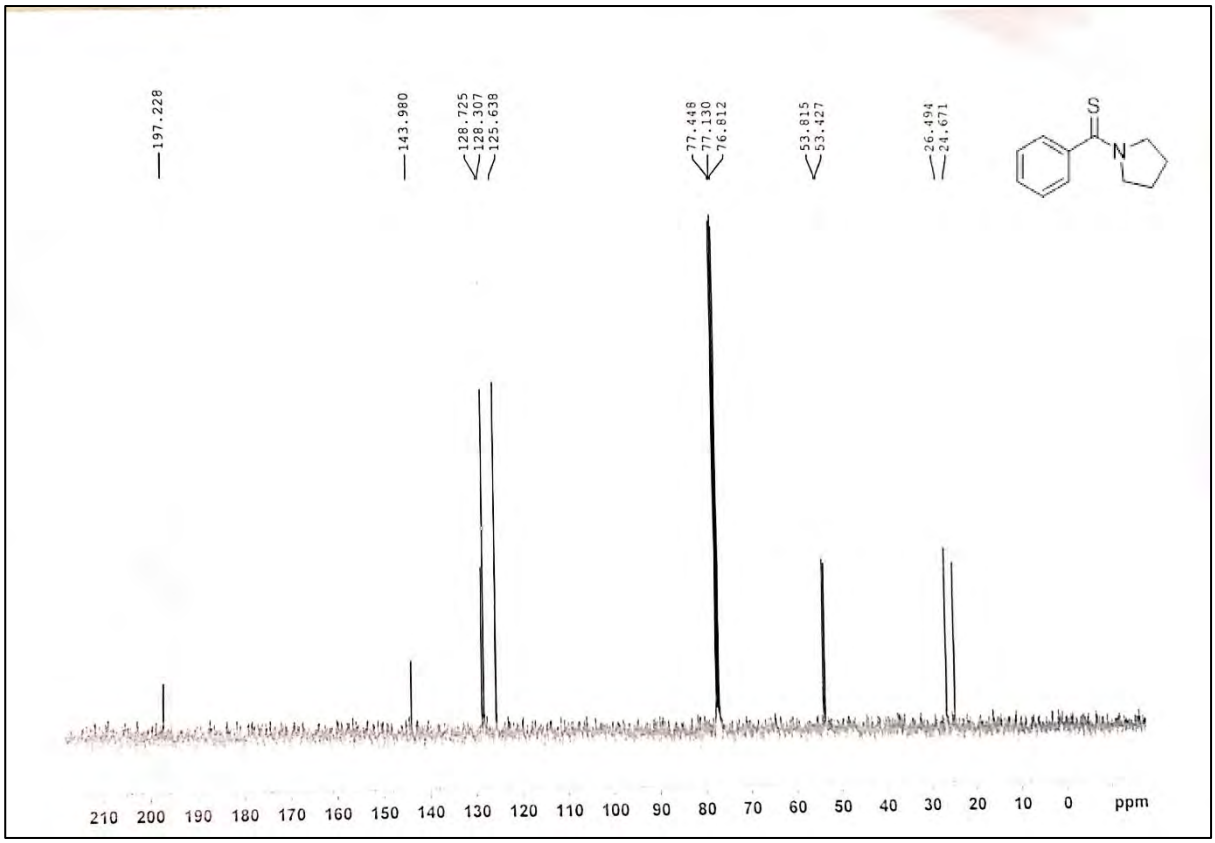


Figure III.4. Scan copy of ^{13}C NMR of Phenyl(pyrrolidin-1-yl)methanethione.

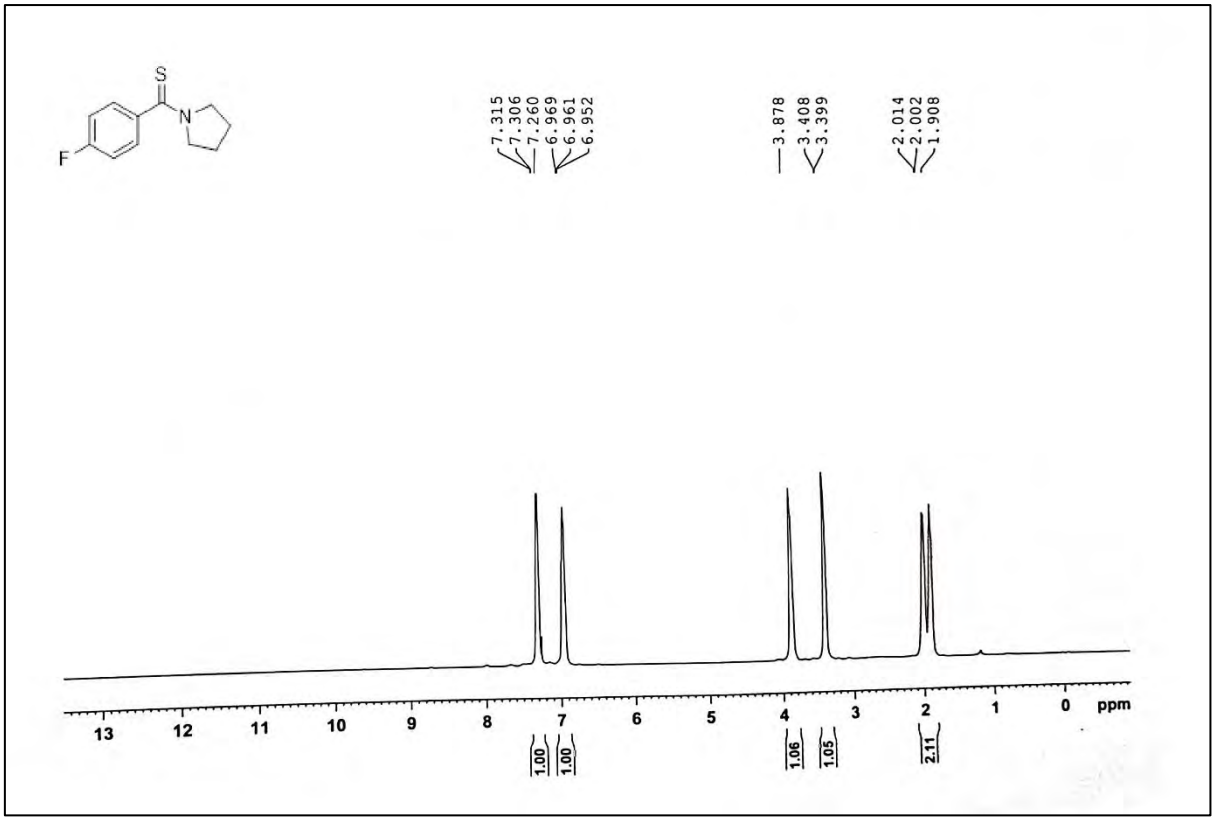


Figure III.5. Scan copy of ^{1}H NMR of (4-fluorophenyl)(pyrrolidin-1-yl)methanethione.

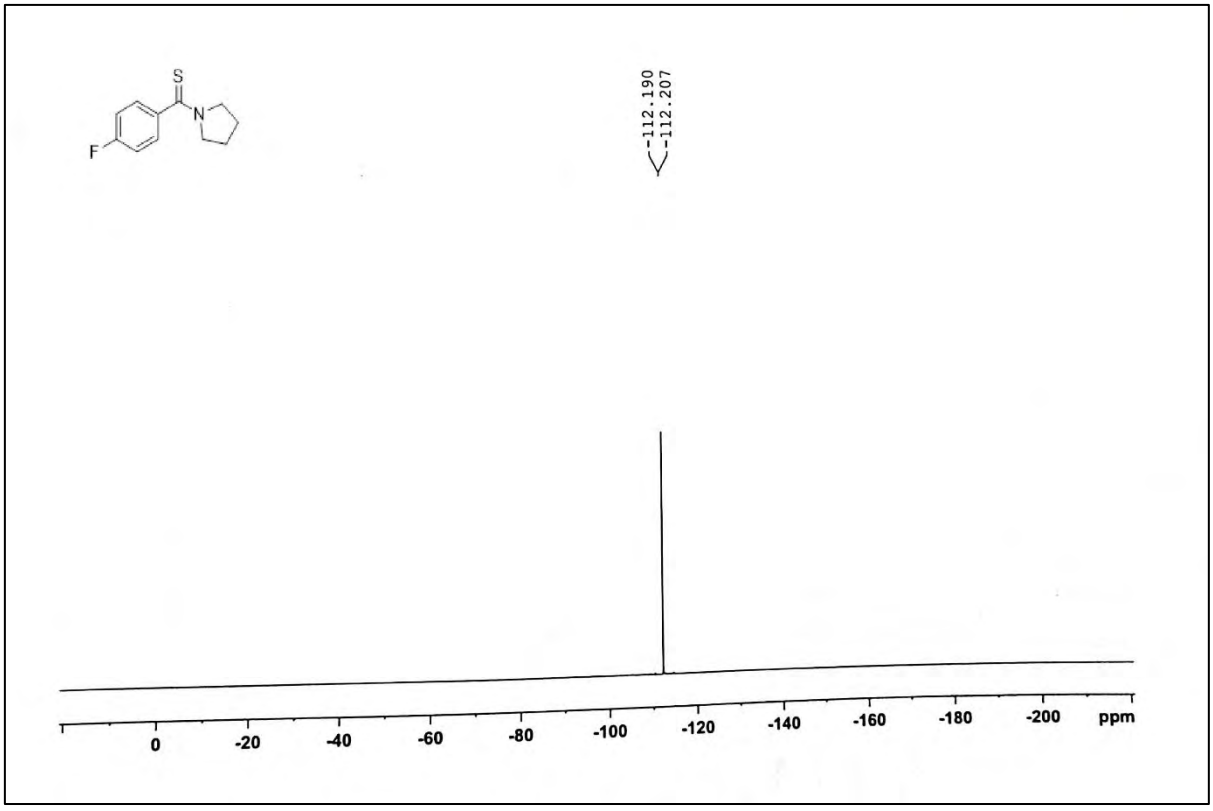


Figure III.6. Scan copy of ^{19}F NMR of (4-fluorophenyl)(pyrrolidin-1-yl)methanethione.

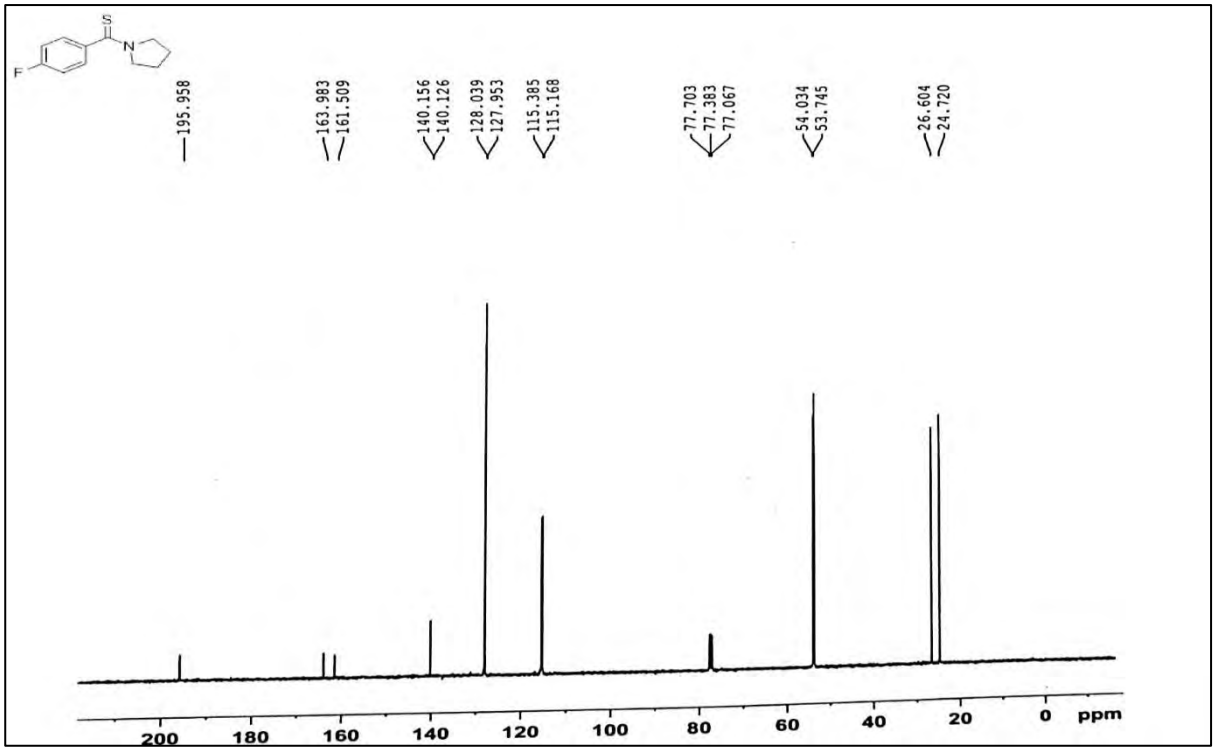


Figure III.7. Scan copy of ^{13}C NMR of (4-fluorophenyl)(pyrrolidin-1-yl)methane.

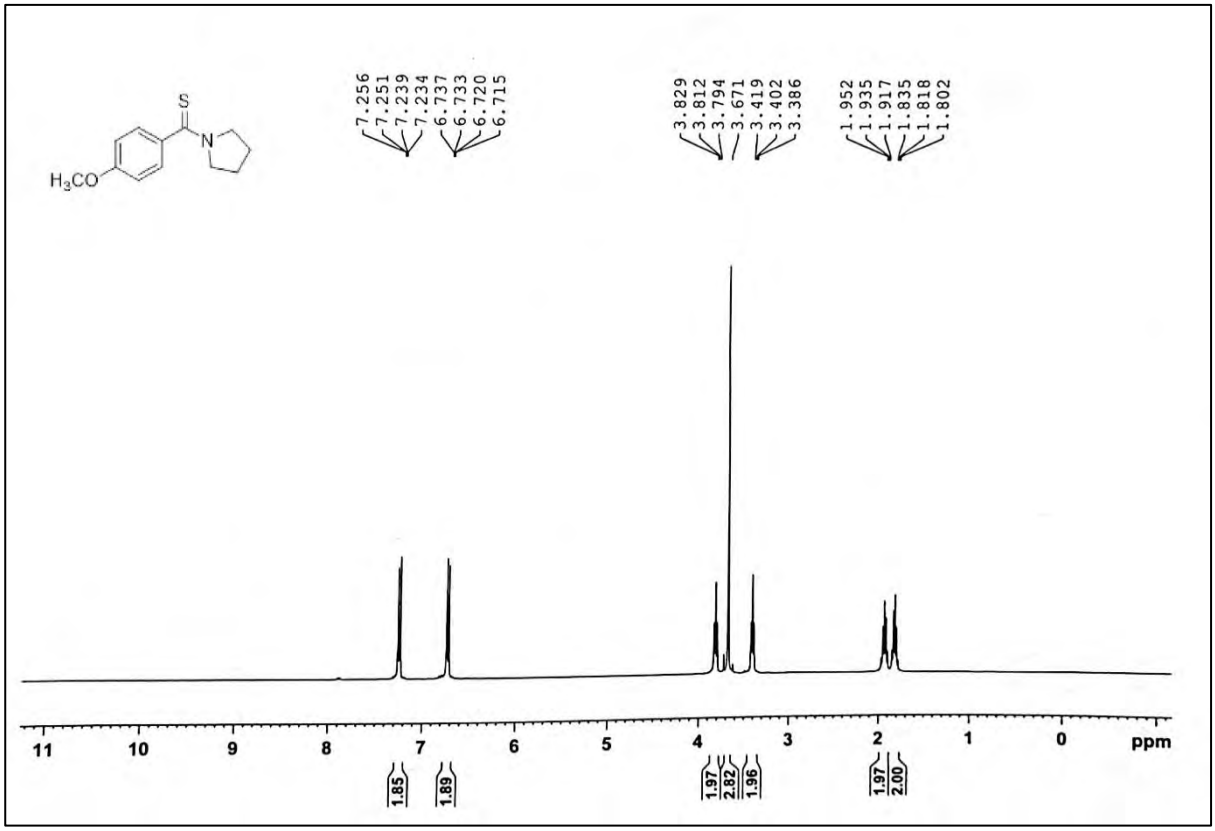


Figure III.8. Scan copy of ^{1}H NMR of (4-methoxyphenyl)(pyrrolidin-1-yl)methanethione.

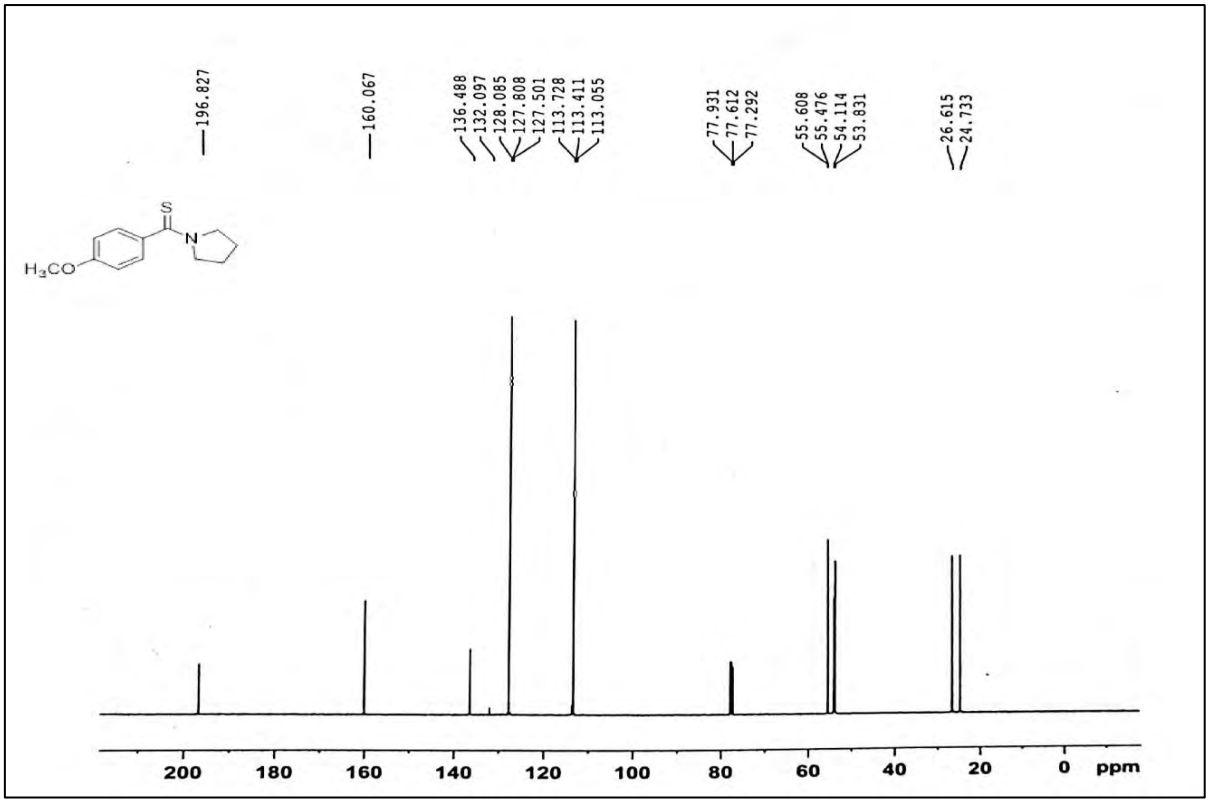


Figure III.9. Scan copy of ^{13}C NMR of (4-methoxyphenyl)(pyrrolidin-1-yl)methanethione.

III.F. Reference

References are given in BIBLOGRAPHY under Chapter III.