CHAPTER 2

Synthesis of 1,2,4-Thiadiazoles and 1,2,4-Selenodiazoles by the Dimerization of Primary Thioamides and Selenoamides

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2.1 Introduction

Sulfur and selenium based organic molecules received significant interest in different fields in the last few decades (Mugesh et al. 2001). 1,2,4-Thiadiazole is an important heterocyclic scaffold found in many drugs, bioactive molecules and natural products (Mayhoub et al. 2012, Li et al. 2013, Romagnoli et al. 2007, shen et al. 2007) (**Figure 2.1**). 1,2,4-Thiadiazoles are privileged building blocks in the synthesis of many bioactive molecules for the treatment of human leukemia (Romagnoli et al. 2007), as cathepsin B inhibitors (Leung et al. 2003), allosteric modulators (Van et al. 2004), factor XIIIa inhibitors (Leung et al. 2005), non-ATP competitive glycogen synthase kinase inhibitors (Martinez et al. 2002), dual 5-lipoxygenase and cyclooxygenase inhibitors (Unangst et al. 1992). In addition, thiadiazole scaffold containing molecules act as G-protein coupled receptors (Ana et al. 2000, Lanzafame et al. 2004, Kohara et al. 1996, Martinez et al. 2000), pesticides and fungicides (e.g. Etridiazole, **Figure 2.1**) (Leung et al. 2005). Therefore, over the decades interest has been maintained in the synthesis of organic compounds having thiadiazoles and selenodiazoles moiety for different fields (Dotsenko et al. 2013, Huang et al. 2003, shen et al. 2007, Pham et al. 2013).

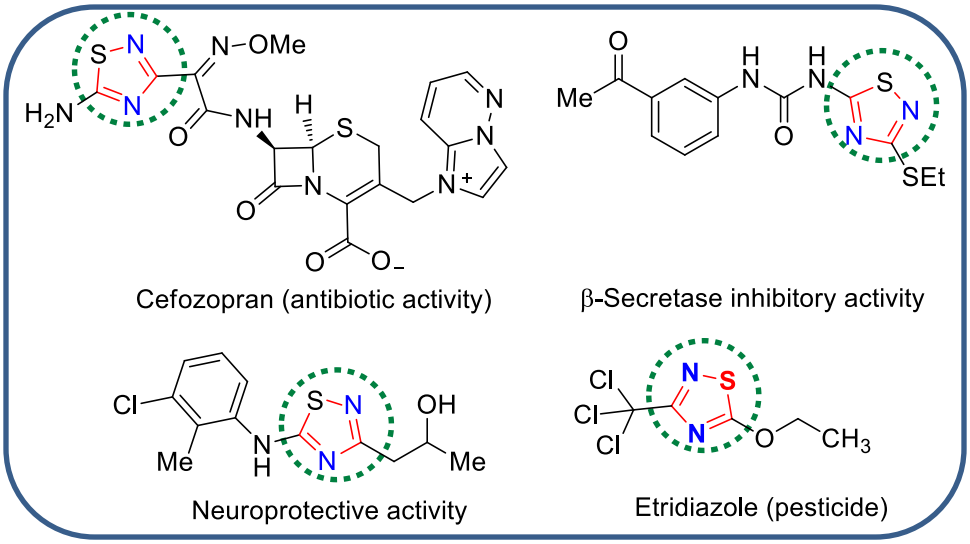
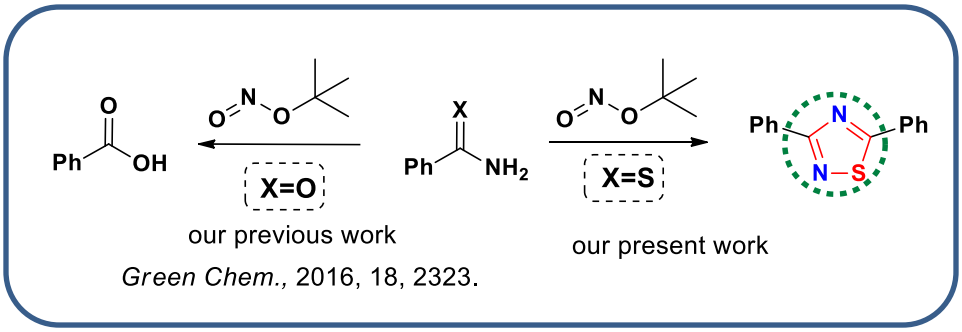


Figure 2.1: Biologically active thiadiazoles.

The simplest approach for the synthesis of 1,2,4-thiadiazoles involves the oxidative dimerization of primary thioamides. This transformation has been achieved using various metal and metal free oxidizing reagents such as ceric ammonium nitrate (CAN) (Vanajatha et al. 2016), 2-iodoxybenzoic acid (IBX) (Patil et al. 2009), bis-acetoxy iodobenzene (BAIB) (Cheng et al. 2002, Mamaeva et al. 2003), *N*-bromosuccinimide (NBS) (Xu et al. 2010), oxone (Yoshimura et al. 2014), nitrous acid (Cronyn et al. 1952), phosphovanadomolybdic acids (Yajima et al. 2014), pentyl pyrediniumtribromide (Zali et al. 2012) etc. However, many of these methods suffer from the use of excess reagents which produces large amounts of by-products, harsh reaction conditions, longer reaction time, tedious workup procedures etc. Therefore, finding a simple and efficient reagent for the dimerization of primary thioamides is of great interest.



Scheme 2.1: Reaction of *tert*-butyl nitrite with benzamide and thiobenzamide.

tert-Butyl nitrite (TBN) is an important synthetic reagent widely used for nitration reactions (Yan et al. 2013, Yan et al. 2014). For example, TBN has been explored for the nitration of phenols, azoarenes, arylboronic acids, acetanilides, sulfanilides etc. under mild reaction conditions (Barral et al. 2007, Marinescu et al. 2003, Zhang et al. 2011, Hao et al. 2015, Koley et al. 2009, Fisher et al. 2016, Majhi et al. 2014, Ji et al. 2015). In addition, TBN has also been explored as a radical initiator for the aerobic cleavage of benzylic carbon–carbon double bonds and triple bonds (Miao et al. 2011, Dutta et al. 2016). TBN is a green, inexpensive and commercially available reagent which can be easily handled and stored.

Our research group is mainly focused on developing simple, efficient and eco-friendly methods for organic transformations (Gupta et al. 2017, Gupta et al. 2017, Chaudhary et al. 2016, Chaudhary et al. 2016, Gupta et al. 2016). In pursuit of this, we have recently reported *N*-nitrosation of secondary amines using *tert*-butyl nitrite under solvent free conditions (Chaudhary et al. 2016). In the same report, we have also disclosed that primary

benzamides undergo hydrolysis to corresponding benzoic acids with *tert*-butyl nitrite in acetic acid (**Scheme 2.1**). In continuation of our previous work, here we would like to disclose an interesting outcome of the reaction between *tert*-butyl nitrite and primary thioamides. In fact, while attempting hydrolysis of thiobenzamide with *tert*-butyl nitrite in acetic acid, a significant amount of dimerized product was observed (**Scheme 2.1**) instead of hydrolysis. This observation spurred us to optimize the reaction condition for obtaining the dimerized product exclusively (**Table 2.1**).

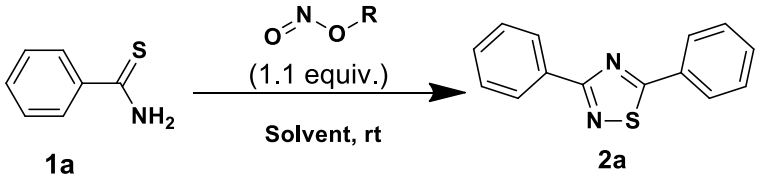
2.2 Results and Discussion

At the outset, the optimization of the dimerization reaction was investigated with thiobenzamide (**1a)** using 1.1 equiv. of TBN in various solvents at room temperature. In acetic acid, the dimerized product **2a** was obtained in 69% yield (**Table 2.1, entry 1**). Similarly, other polar protic solvents such as methanol, ethanol, *iso*-propanol, *tert*-butanol and water gave the desired product in 65-90% yield within the period of 30-60 min (**Table 2.1, entries 2-6**).

On the other hand, dimerization was achieved efficiently in various aprotic solvents such as dichloromethane, chloroform, acetonitrile, tetrahydrofuran, benzene and toluene in short span of time at room temperature (**Table 2.1, entries 7-12**). Among them, dichloromethane gave the desired product, i.e. 3,5-diphenyl-1,2,4-thiadiazole (**2a**) in 95% yield within 5 min (**Table 2.1, entry 7**). Further optimization was continued with other alkyl nitrites such as *iso*-amyl nitrite (IAN) and *n*-butyl nitrite (NBN) at room temperature.

Both the reagents gave the desired product in good yield but they require slightly longer time (*i.e.* 15 min) for completion of the reaction (**Table 2.1, entries 13 and 14**). Formation of model compound **2a** is confirmed by the ^{1}H & ^{13}C NMR spectroscopy (**Figure 2.2** and **2.3**).

Table 2.1: Optimization of dimerization of thiobenzamide[a]



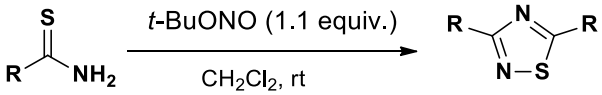
Entry	Solvent	Reagent	Time	Yield[b] (%)
1	CH_3COOH	TBN	30	69
2	CH_3OH	TBN	30	90
3	C_2H_5OH	TBN	40	89
4	*iso*-Propanol	TBN	40	85
5	*tert*-butanol	TBN	60	79
6	H_2O	TBN	60	65
7	CH_2Cl_2	TBN	5	95
8	$CHCl_3$	TBN	10	90
9	CH_3CN	TBN	15	89
10	THF	TBN	15	89
11	Benzene	TBN	15	70
12	Toluene	TBN	15	70
13	CH_2Cl_2	IAN[c]	15	93
14	CH_2Cl_2	NBN[d]	15	92

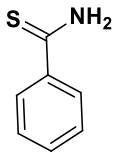
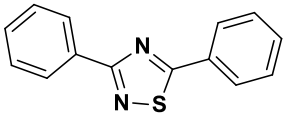
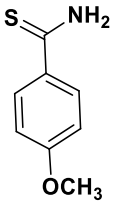
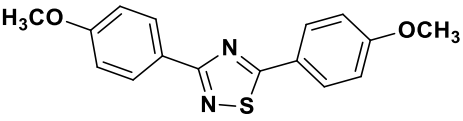
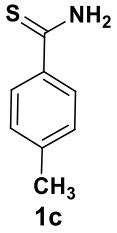
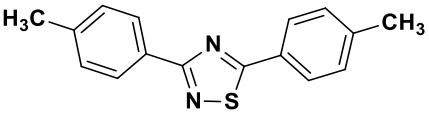
[a] **Reaction conditions**: Benzothioamide (1.0 mmol) and TBN were stirred in the respective solvents (2 mL) at room temperature, [b] Isolated yields, [c] IAN: *iso*-amyl nitrite, [d] NBN: *n*-butyl nitrite.

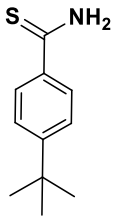
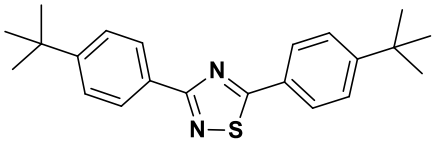
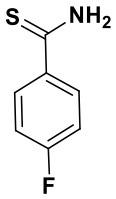
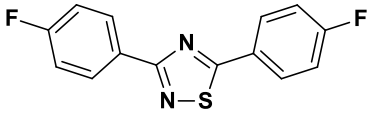
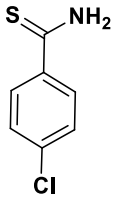
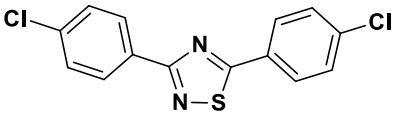
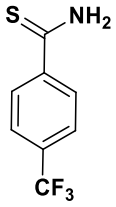
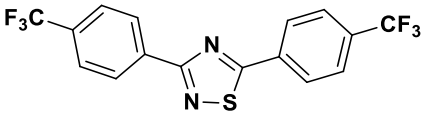
Having established the optimized condition, we examined the oxidative dimerization of various substituted thiobenzamides using *tert*-butyl nitrite in dichloromethane to explore the scope of substrates amenable to this method (**Table 2.2**). Electron donating groups such as methoxy (**1b**), methyl (**1c**) and *tert*-butyl substituted (**1d**) thiobenzamides were successfully dimerized to give product 3,5 bis(4-methoxyphenyl)-1,2,4-thiadiazole (**2b**), 3,5-dip-tolyl-1,2,4-thiadiazole (**2c**), 3,5-bis(4-*tert*-butylphenyl)-1,2,4-thiadiazole (**2d**) respectively, in excellent yields within 5 min (**Table 2.2**, **entries 2-4**). Similarly, dimerization of halogen substituted thiobenzamides such as 4-fluoro (**1e**) and chloro-thiobenzamides (**1f**) was successfully accomplished to obtain the desired products 3,5-bis(4-fluorophenyl)-1,2,4-thiadiazole (**2e**) and 3,5-bis(4-chlorophenyl)-1,2,4-thiadiazole (**2f**) (**Table 2.2, entries 5, 6**) in >89% yield.

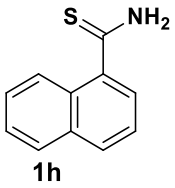
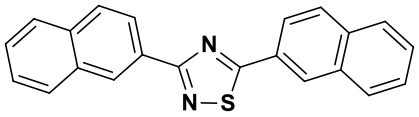
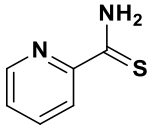
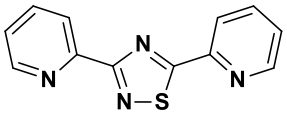
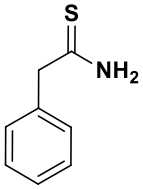
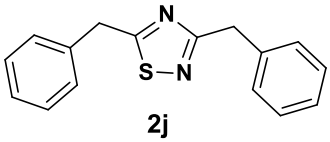
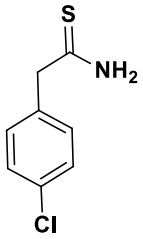
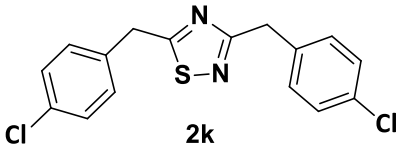
Further, the analogue possessing the strongly electron withdrawing trifluoromethyl (**1g**) group was subjected to the dimerization under optimized condition. To our delight, the substrate **1g** underwent dimerization smoothly and gave the desired product 3,5-bis(trifluoromethyl)phenyl-1,2,4-thiadiazole (**2g**) in 89% yield. However it requires 30 min (**Table 2.2, entry 7**). Likewise, 2-naphthyl thiobenzamide (**1h**) was successfully dimerized to 3,5-dinaphthyl 1,2,4-thiadiazoles (**2h**) in 82% yield (**Table 2.2, entry 8**).

Table 2.2: Dimerization of thioamides using *tert*-butyl nitrite[a]



Entry	Substrate	Product	Time (min)	Yield[b] (%)
1	 1a	 2a	5	95
2	 1b	 2b	5	94
3	 1c	 2c	5	92

4	 1d	 2d	5	83
5	 1e	 2e	15	89
6	 1f	 2f	15	90
7	 1g	 2g	30	89

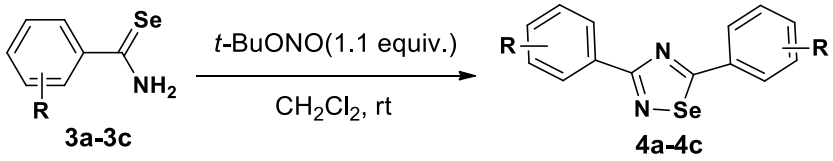
8	 1h	 2h	5	82
9	 1i	 2i	5	88
10	 1j	 2j	5	85
11	 1k	 2k	5	82

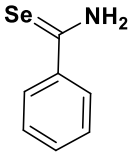
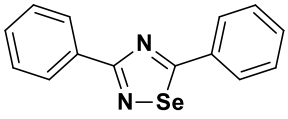
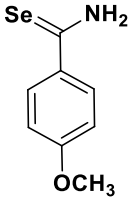
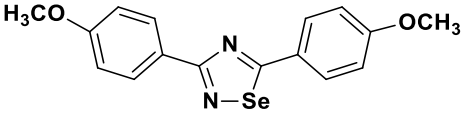
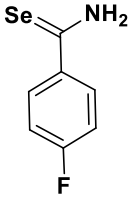
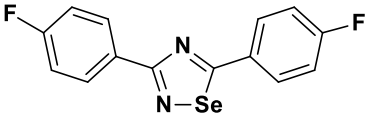
[a] **Reaction conditions:** Substrate (1.0 mmol) and *tert*-butyl nitrite (TBN) (1.1 equiv.) were stirred in dichloromethane (2 mL) at room temperature. [b] Isolated yields.

To our surprise, the optimized condition was also found to be suitable for the oxidative dimerization of heterocyclic thiobenzamide such as pyridine-2-carbothioamide (**1i**). The reaction proceeded smoothly to provide the 3,5-di(pyridin-2-yl)-1,2,4-thiadiazole (**2i**) in 88% yield within 5 minute (**Table 2.2, entry 9**). After the extensive study with thiobenzamides, oxidative dimerization of phenylethanethioamide *viz.* 2-phenylethanethioamide (**1j**) and 2-(4-chlorophenyl)ethanethioamide (**1k**) was investigated. The corresponding dimerized products, 3,5-dibenzyl-1,2,4-thiadiazole (**2j**) and 3,5-bis(4-chlorobenzyl-1,2,4-thiadiazole (**2k**) (**Table 2.2, entries 10 and 11**) were obtained in excellent yields demonstrating the broad scope of the current methodology.

Encouraged by the results obtained from dimerization of thioamides, we have attempted the oxidative dimerization of benzoselenoamide (**3a**) to 1,2,4-selenadiazole using *tert*-butyl nitrite (**Table 2.3**). For this study, differently substituted benzoselenoamides *viz.* benzoselenoamides (**3a**), 4-methoxybenzoselenoamide (**3b**) and 4-fluorobenzoselenoamide (**3c**) were prepared and subjected to dimerization under the optimized condition. To our delight, corresponding 3,5-disubstituted 1,2,4-selenadiazoles *viz*. 3,5-diphenyl-1,2,4–selenadiazole (**4a**), 3,5-bis(4-methoxyphenyl)-1,2,4-selenadiazole (**4b**) and 3,5-bis(4-fluorophenyl)-1,2,4-selenadiazole (**4c**) (**Table 3.3, entries 1-3**) were obtained in good yields within the period of 15-20 min which serves to extend the scope of the present methodology.

Table 2.3: Dimerization of benzoselenoamide using *ter*t-butyl nitrite[a]



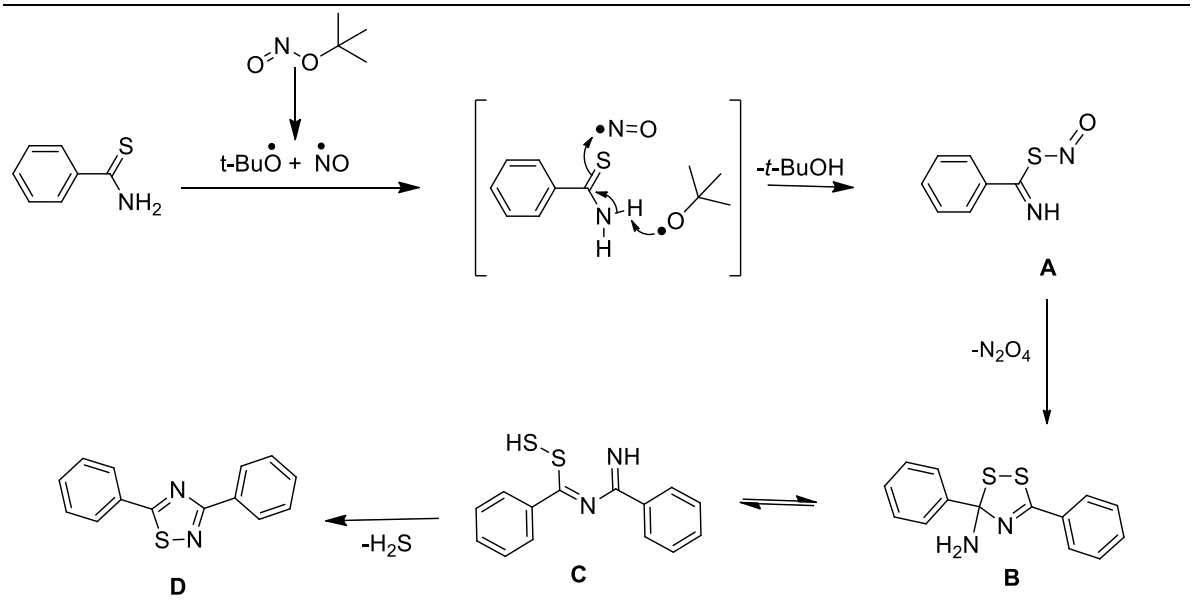
Entry	Substrate	Product	Time (min)	Yield[b] (%)
1	 3a	 4a	15	89
2	 3b	 4b	15	87
3	 3c	 4c	20	80

[a]**Reaction conditions:** Substrate (1.0 mmol) and *tert*-butyl nitrite (TBN) (1.1 equiv.) were stirred in dichloromethane (2 mL) at room temperature. [b] Isolated yields.

Overall, this practical metal-free approach shows good functional group tolerance while the desired products were obtained in excellent yields. ^{1}H & ^{13}C NMR spectra of 1,2,4-selenadiazole (**4a**) have been given in **Figure** 2.4 & 2.5.

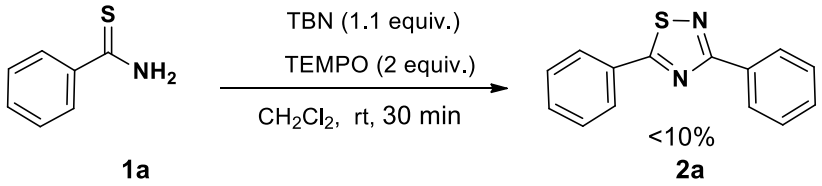
2.3 Mechanistic Studies and Control Experiment

A proposed mechanism for the TBN induced dimerization reaction is shown in **Scheme 2.2**. TBN undergoes radical dissociation to form *t*-butoxy and nitroso radicals which may react with thiobenzamide to form intermediate **A**. Further, this intermediate may undergo dimerization via elimination of dinitrogen tetroxide (N_2O_4) to form intermediate **B** which may be in equilibrium with intermediate **C**. Further, the intermediate **C** might release hydrogen sulfide (H_2S) to yield the desired product **D**.



Scheme 2.2: Proposed mechanism for the TBN induced dimerization reaction.

To support our mechanistic hypothesis, the dimerization reaction was carried out with a radical trapping reagent TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl). The experiment was performed with 2 equiv. of TEMPO under optimized conditions in dichloromethane at room temperature (**Scheme 2.3**). As expected, the dimerization process was inhibited by TEMPO with less than 10% of the desired product (*i.e.* 3,5-diphenyl-1,2,4-thiadiazole) observed.

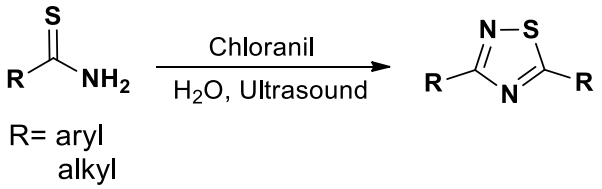


Scheme 2.3: Control experiment with TEMPO.

2.4 Development of another Methodology

Despite having many advantage of our previously reported method, there is still scope to developed another methodology for the synthesis of biologically important 1,2,4-thiadiazole moiety under environmentally benign condition. In the previous protocol, reaction has been performed in dichloromethane as a solvent but it is volatile organic solvent. Hence, in the continuation of our pervious method, we have developed another methodology for the synthesis of 1,2,4-thiadiazole derivatives in a greener way by replacing organic solvent to the greener solvent under non-conventional energy source. In

the present protocol, we have performed the reaction under ultrasound irradiation method in aqueous medium using chloranil as an oxidizing reagent (**Scheme 2.4**).



Scheme 2.4: Chloranil mediated synthesis of 1,2,4-thiadiazole derivatives.

The use of appropriate solvent in organic synthesis is also very important from the green chemistry point of view. In this regard the use of water as solvent has attracted great deal of interest in recent years. Water is the solvent of choice not only from an ecological point of view but also from an economic point of view because it is cheap, abundantly available, non-toxic and non-flammable and more selective than organic solvents. Water acts differently from other organic solvents in terms of its distinctive and unusual physical and chemical properties (Gawande et al. 2013, Lindstrom et al. 2008).

In this context, ultrasound assisted reactions have gained much attention because they offer several advantages such as milder reaction condition, higher reaction rate, excellent yield and low energy consumption. Many organic transformations have been successfully achieved with the help of ultrasound irradiation method as compared to conventional methods. The increasing requirement for environmentally clean technology that reduces production of waste source, long reaction time, high temperature and unsatisfactory yield prompt us to use the ultrasound irradiation method. Ultrasound wave improves the rate of

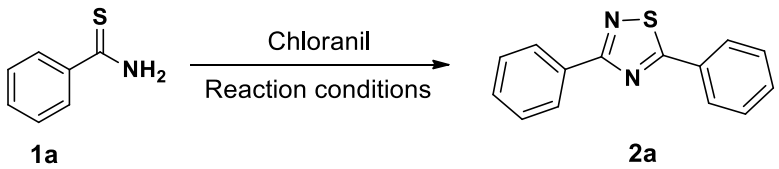
chemical reaction via the process of acoustic cavitation. Therefore, ultrasound assisted organic synthesis, as a green synthetic approach is considered as a powerful technique (Ghomi et al. 2018, Nishtala et al. 2017, Banerjee et al. 2017).

Chloranil is an expedient oxidant in organic chemistry and has extensive application in dehydrogenation reactions particularly suitable for aromatization of hydro aromatic substances (Jackman et al. 1960, Becker et al. 1974) and successful utilization in the synthesis of nitrogen (Landberg et al. 1975, Huisgen et al. 1962) and sulphur (Mcintosh et al. 1975, Tilak et al. 1964) containing heterocycles. Chloranil is used in selective oxidation of organic molecule by hydride abstraction mechanism (Wendlandt et al. 2015). It also undergoes facile nucleophilic displacement reaction with 1° and 2° amine leading to the formation of 2,5-bis amino derivatives and reaction proceed via one electron oxidation of amine (Foster et al. 1966). Chloranil is inexpensive, nontoxic and air stable which makes it easy to handle. The fascinating nature of water and beneficial effects of ultrasound technique encouraged us to undertake the synthesis of 1,2,4-thiadiazole derivatives without catalyst under benign conditions.

2.4.1 Optimization of Reaction Condition with Chloranil

The reaction conditions were first optimized using equimolar amounts of thiobenzamide (**1a**) as a test substrate and chloranil. The reaction was carried out in H_2O while stirring at room temperature for 3 h and yielded only 20% of product **2a**.

Table 2.4: Effect of reaction conditions on the yield of model compound **2a**[a]



1a **2a**

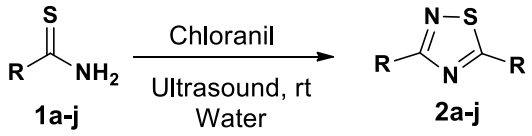
Entry	Reaction conditions	Solvent	Time	Yield[b] (%)
1	Stirring, rt	H_2O	3 h	20
2	Stirring, reflux	H_2O	3 h	40
3	50 °C	Solvent-free	3 h	50
4	80 °C	Solvent-free	3 h	70
5	120 °C	Solvent-free	3 h	70
6	**Ultrasound (US), rt**	**H_2O**	**3 min**	**95**
7	US, rt	MeCN	5 min	75
8	US, rt	THF	10 min	70
9	US, rt	EtOH	15 min	85
10	US, rt	1,4-Dioxane	12 min	65
11	US, rt	$CHCl_3$	8 min	78
12	US, rt	CH_2Cl_2	9 min	79
13	US, rt	DCE	7 min	82
14	US, rt	DMSO	10 min	78
15	US, rt	PhH	12 min	71
16	US, rt	PhMe	15 min	75

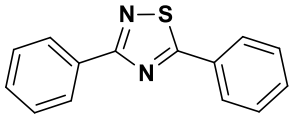
[a] **Reaction conditions**: Thiobenzamide (1.0 mmol), chloranil (1.1 mmol), solvent (3 mL).
[b] Isolated yield.

In the second run, the reaction mixture was refluxed for 3 h which gave low yield of the desired product (**Table 2.3, entry 2**). Further on heating the reaction mixture by conventional method at 50, 80 and 120 °C under solvent-free condition gave the desired product in 50–70% yield after 3 h (**Table 2.3, entries 3–5**). In order to improve the yield of the product, the reaction was performed under ultrasound irradiation at room temperature in H_2O. To our surprise, 95% yield was obtained in 3 min. To investigate the effect of solvents, the reaction was carried out in different polar and nonpolar solvents. Although the desired product was obtained in both polar (H_2O, MeCN, THF, EtOH, 1,4-dioxane, $CHCl_3$, CH_2Cl_2, DCE, DMSO) and nonpolar solvents (PhH, PhMe), H_2O was found to be the best solvent for the dimerization.

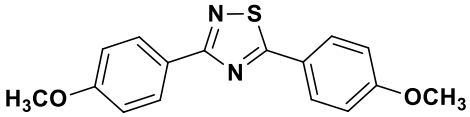
With optimized reaction conditions, the applicability of this methodology was examined with the different primary thiobenzamide derivatives and the results are summarized in Table 2.4. These reaction conditions with chloranil as oxidant show extensive functional group tolerance and prove to be a general method for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles. It was found that the reaction proceeds smoothly and provides an excellent yield of desired product *viz.* 3,5-bis(4-methoxyphenyl)-1,2,4-thiadiazole (**2b**), 3,5-dip-tolyl-1,2,4-thiadiazole (**2c**), 3,5-bis(4-*tert*-butylphenyl)-1,2,4-thiadiazole (**2d**), 3,5-bis(4-nitrophenyl)-1,2,4-thiadiazole (**2l**) within short period of time using thiobenzamide with electron-donating (methoxy **(1b)**, methyl (**1c**) and *tert*-butyl (**1d**) substituted or electron-withdrawing substituent (nitro) (**1l**).

Table 2.5: Synthesis of thiadiazoles derivatives **2a–j**[a]

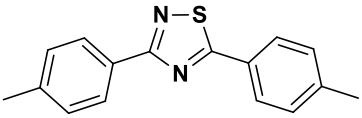




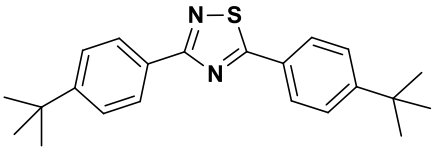
2a, 3 min, 95%[b]



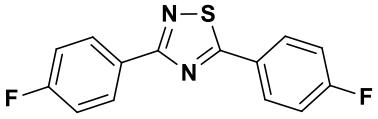
2b, 5 min, 94%



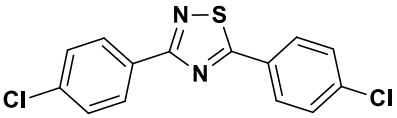
2c, 6 min, 95%



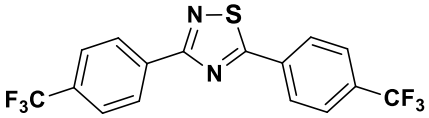
2d, 8 min, 89%



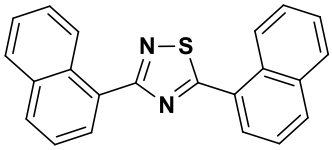
2e, 6 min, 90%



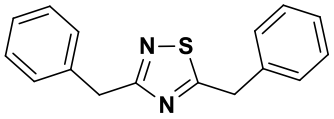
2f, 7 min, 88%



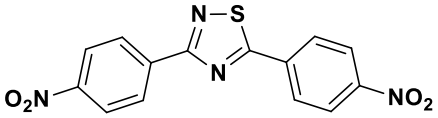
2g, 6 min, 91%



2h, 5 min, 87%



2j, 5 min, 87%



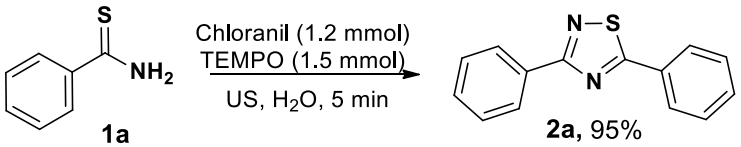
2l, 8 min, 94%

[a] **Reaction conditions:** substrate (1.0 mmol) and chloranil (1.1 mmol) were irradiated with ultrasound in H_2O (3 mL) at room temperature. [b]Isolated yield.

Interestingly, thiobenzamide bearing halogen substituents such as fluorine, chlorine, and trifluoro could also be reacted in efficient manner to obtain the desired products *viz*. products 3,5-bis(4-fluorophenyl)-1,2,4-thiadiazole (**2e**), 3,5 bis (4-chlorophenyl)-1,2,4-thiadiazole (**2f**) and 5-bis(trifluoromethyl)phenyl-1,2,4-thiadiazole (**2g**) in good yield. Likewise, naphthalene-1-carbothioamide (**1h**) was successfully transferred into 3,5-di(naphthalen-1-yl)-1,2,4-thiadiazole (**2h**) in 87% yield (**Table 2.5**) within few minutes. The results established that no significant electronic and steric effects of the substituents on the phenyl ring were observed. This reaction also gave good yield for 3,5-dibenzyl-1,2,4-thiadiazole (**2j)** (**Table 2.5**). The corresponding products were obtained in good yield which show the wide scope of current methodology.

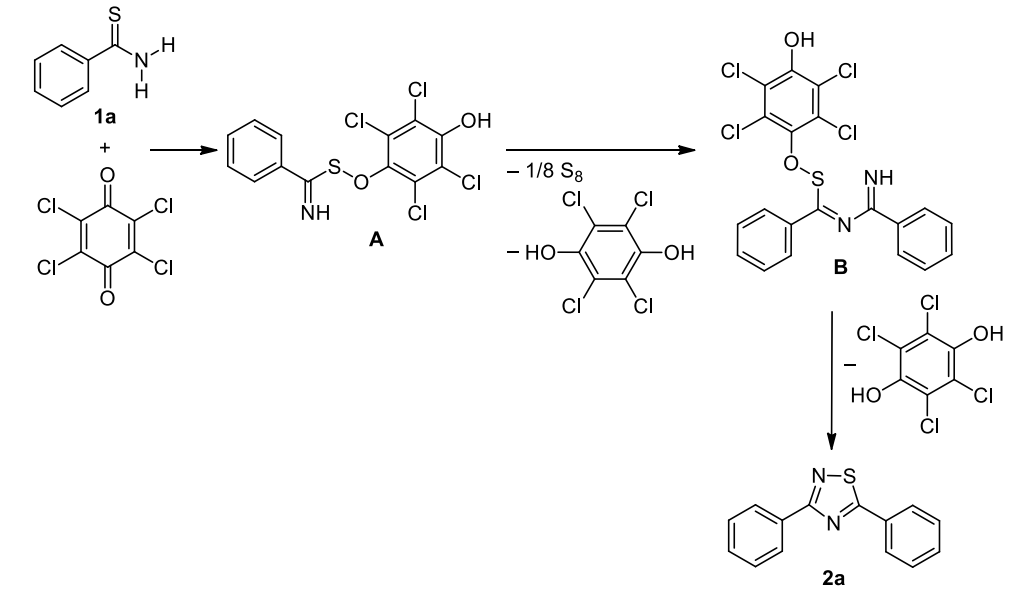
2.5 Mechanistic Studies and Control Experiment with TEMPO

A control experiment was performed using (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as radical trapping agent and it was observed that TEMPO does not quench the reaction. This shows that reaction does not proceed via radical intermediate and a nucleophilic pathway has been proposed (**Scheme 2.5**).



Scheme 2.5: Controlled experiment with TEMPO.

On the basis of product analysis, a mechanism for the chloranil-assisted dimerization of primary thiobenzamide is proposed in Scheme 2.6. Oxidative addition of thioamide **1a** to chloranil leads to intermediate **A** which dimerizes forming intermediate **B**. Product **2a** is formed after cyclization of intermediate **B**.



Scheme 2.6: Proposed mechanism for the chloranil-mediated synthesis of 1,2,4-thiadiazoles.

2.6 Experimental Section

2.6.1 Experimental procedure for the dimerization of benzothioamides using TBN

The primary thioamides (**1a**-**1k**) (1.0 mmol) was stirred in dichloromethane (2 mL) at room temperature to which 1.1 equiv. of *tert*-butyl nitrite (TBN) was added. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted

with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and subjected for silica gel (60-120 mesh) column chromatography purification (SiO_2: hexane–EtOAc) to obtain the desired products (**2a**-**2k**).

2.6.2 Experimental procedure for the dimerization of benzoselenoamide

The primary benzoselenoamides (**3a**-**3c**) (1.0 mmol) was stirred in dichloromethane (2 mL) at room temperature to which 1.1 equiv. of *tert*-butyl nitrite (TBN) was added. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and subjected for silica gel (60-120 mesh) column chromatography purification (SiO_2: hexane–EtOAc) to obtain the desired products (**4a**-**4c**).

2.6.3 Experimental procedure for control experiment with TEMPO

The thiobenzamide (**1a**) (1.0 mmol) and TEMPO (2.0 mmol) was stirred in dichloromethane (2 mL) at room temperature for 10 min to which 1.1 equiv. of *tert*-butyl nitrite (TBN) was added. The reaction was further stirred for 30 min and diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and subjected for silica gel (60-120 mesh) column chromatography purification (SiO_2: hexane–EtOAc) to obtain **2a**.

2.6.4 Experimental procedure for the dimerization of benzothioamides using chloranil

A flask was charged with primary thiobenzamide **1a–1l** (1.0 mmol) and chloranil (1.1 mmol) in H_2O (3 mL). The reaction mixture was irradiated with ultrasound at room temperature for appropriate time. The progress of reaction was monitored with TLC. After completion of the reaction, solvent was concentrated under reduced pressure and the obtained residue was subjected to silica gel column chromatography purification (hexane–EtOAc) to obtain the desired products.

2.7 Analytical Data

2.7.1 3,5- Diaryl -1,2,4- thiadiazoles (2a): The title compound was obtained as white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.59; (Yield: 226 mg (95%) in both TBN and chloranil); m.p. 90 °C; **IR** (neat) 3050, 2922, 1599, 1464, 1407, 1315, 1270, 1171, 751 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.32 (dd, 2H), 7.98 (dd, 2H), 7.48–7.40 (m, 6H); **^{13}C NMR** (125 MHz, CDCl3) δ (ppm): 188.1, 173.8, 132.8, 131.9, 130.7, 130.3, 129.2, 128.6, 128.3, 127.4.; **HRMS**: Calc. for $C_{14}H_{11}N_2S$ $[M+H]^+$: 239.0643, Obser: 239.0698.

2.7.2 3,5 Bis(4-methoxyphenyl)-1,2,4-thiadiazole (2b): The title compound was obtained as pale yellow solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); R_f = 0.60; (Yield: 280 mg (94%) in both TBN and chloranil); m.p. 138-140 °C; **IR** (neat) 2990, 2872, 1632, 1443, 1255, 1295, 1032, 835 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.24 (d, 2H), 7.91 (d, 2H), 6.93 (d, 4H), 3.81 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 187.3, 173.3, 162.4, 161.2, 129.8, 129.1, 126.0, 123.6, 114.5, 113.9, 55.4, 55.3; **HRMS**: Calc. for $C_{16}H_{15}N_2O_2S$ $[M+H]^+$: 299.0854, Obser: 299.0858.

2.7.3 3,5-Dip-tolyl-1,2,4-thiadiazole (2c): The title compound was obtained as white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.55; (Yield: 245mg (92%) in TBN, 253 mg (95%) in chloranil); m.p. 135-137 °C; **IR** (neat) 2962, 1915, 1402, 1317, 1011, 842, 735 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.20 (d, 2H), 7.86 (d, 2H), 7.24 (t, 4H), 2.36 (d, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 187.9, 173.7, 142.4, 140.4, 130.3, 129.9, 129.3, 128.2, 128.1, 127.4, 21.6, 21.5; **HRMS**: Calc. for $C_{16}H_{15}N_2S$ $[M+H]^+$: 267.0956, Obser: 267.0953.

2.7.4 3,5-Bis(4-*tert*-butylphenyl)-1,2,4-thiadiazole (2d): The title compound was obtained as white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.52; (Yield: 290 mg (83%) in TBN, 312 mg (89%) in chloranil); m.p. 91-93 °C; **IR** (neat) 2974, 2905, 1724, 1609, 1472, 1495, 1323, 1134, 835 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.34 (d, 1H), 8.00 (d, 1H), 7.61 (d, 1H), 7.55 (dd, 3H), 7.50 (d, 2H), 1.40 (s, 9H), 1.35 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 187.7, 173.7, 156.5, 155.4, 153.5, 131.9, 130.2, 128.0, 127.2, 126.1, 125.5, 35.2, 34.8, 31.2, 30.9; **HRMS**: Calc. for $C_{22}H_{27}N_2S$ $[M+H]^+$: 351.1895, Obser: 351.1904.

2.7.5 3,5-Bis(4-fluorophenyl)-1,2,4-thiadiazole (2e): The title compound was obtained as a white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.54; (Yield: 244 mg (89%) in TBN, 246 mg (90%) in chloranil); m.p. 185-187 °C; **IR** (neat) 2926, 2855, 1741, 1547, 1514, 1463, 1226, 835, 739 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.37 (dd, 2H), 8.05 (dd, 2H), 7.25–7.14 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 186.9, 172.7, 165.9, 163.9, 130.4, 129.6, 129.5, 129.0, 127.0, 116.6, 115.8; **HRMS**: Calc. for $C_{14}H_9F_2N_2S$ $[M+H]^+$: 275.0455, Obser: 275.0455.

2.7.6 3,5 Bis (4-chlorophenyl)-1,2,4-thiadiazole (2f): The title compound was obtained as a white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.55; (Yield: 276 mg (90%) in TBN, 270 mg (88%) in chloranil); m.p. 161-162 °C; **IR** (neat) 2925, 1741, 1464, 1424, 1091, 1013, 829, 738 cm-1; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.31 (d, 2H), 7.98 (d, 2H), 7.49 (dd, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 187.0, 172.8, 138.1, 136.5, 131.1, 129.6, 129.6, 128.9, 128.6; **HRMS**: Calc. for $C_{14}H_9Cl_2N_2S$ $[M+H]^+$: 306.9863, Obser: 306.9865.

2.7.7 3,5-Bis(trifluoromethyl)phenyl-1,2,4-thiadiazole (2g): The title compound was obtained as white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.56; (Yield: 332 mg (89%) in TBN, 340 mg (91%) in chloranil); m.p. 81 °C; **IR** (neat) 2927, 1742, 1469, 1319, 1268, 1128, 1063, 894

cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.52 (d, 1H), 8.19 (d, 1H), 7.80 (dd, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 186.9, 172.6, 135.5, 133.7, 132.3, 128.6, 127.9, 127.8, 126.4, 125.7, 124.6, 122.8; **HRMS**: Calc. for $C_{16}H_9F_6N_2S$ $[M+H]^+$: 375.0391, Obser: 375.0412.

2.7.8 3,5 Di(naphthalalen-1-yl)-1,2,4-thiadiazole (2h): The title compound was obtained as a white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.52; (Yield: 277 mg (82%) in TBN, 294 mg (87%) in chloranil); m.p. 120-121 °C; **IR** (neat) 3040, 2925, 2359, 1722, 1476, 1384, 1241, 1049, 795, 761 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 9.29 (d, 1H), 9.00 (d, 1H), 8.55 (dd, 1H), 8.27 (d, 1H), 8.10–8.05 (m, 4H), 7.99 (d, 1H), 7.93 (s, 1H), 7.71 (s, 1H), 7.63 (s, 1H), 7.54–7.50 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 186.8, 173.8, 134.0, 133.9, 133.1, 132.5, 131.0, 130.9, 130.1, 129.9, 129.8, 129.1, 128.5, 128.5, 128.5, 128.4, 127.9, 127.5, 127.1, 126.6, 126.3, 126.0, 125.1, 124.8; **HRMS**: Calc. for $C_{22}H_{15}N_2S$ $[M+H]^+$: 339.0956, Obser: 339.0965.

2.7.9 3,5-Di(pyridine-2-yl)-1,2,4-thiadiazole (2i): The title compound was obtained as a yellow solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.60; (Yield 211 mg (88%) in TBN); m.p. 134 °C; **IR** (neat) 2921, 2851, 1725, 1496, 1433, 1244, 1036, 896 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.71 (d, 2H), 8.53 (d, 2H), 7.85 (d, 2H), 7.49–7.44 (m, 2H); **^{13}C NMR** (125 MHz,

$CDCl_3$) δ (ppm): 196.0, 150.6, 149.4, 147.3, 141.2, 137.3, 134.8, 126.5, 126.3, 125.2, 120.6, 96.2; **HRMS**: Calc. for $C_{12}H_9N_4S$ $[M+H]^+$: 241.0548, Obser: 241.0556.

2.7.10 3,5-Dibenzyl-1,2,4-thiadiazole (2j): The title compound was obtained as yellow oil. The Residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5), R_f = 0.63; (Yield: 226 mg (85%) in TBN, 231 mg (87%) in chloranil); **IR** (neat) 3089, 1590, 1398, 1032, 832 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.41–7.39 (m, 2H), 7.36-7.33 (m, 6H), 7.29–7.26 (m, 2H), 4.38 (s, 2H), 4.33 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 192.2, 175.5, 137.1, 136.1, 129.0, 128.5, 127.7, 126.7, 39.2, 37.8; **HRMS**: Calc. for $C_{16}H_{15}N_2S$ $M+H]^+$: 267.0956, Obser: 267.0957.

2.7.11 3,5-Bis(4-chlorobenzyl-1,2,4-thiadiazole (2k): The title compound was obtained as yellow solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5), R_f = 0.60; (Yield 274 mg (82%) in TBN); m.p. 60-62 ^oC; **IR** (neat) 3034, 1542, 1322, 1101, 890 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.37 (s, 1H), 7.34–7.25 (m, 7H), 4.34 (s, 2H), 4.28 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 191.5, 175.2, 135.4, 134.4, 133.7, 132.7, 130.4, 130.3, 129.2, 128.7, 38.5, 37.0; **HRMS**: Calc. for $C_{16}H_{13}C_{l2}N_2S$ $[M+H]^+$: 335.0176, Obser: 335.0174.

2.7.12 3,5-Bis(4-nitrophenyl)-1,2,4-thiadiazole (2l): The title compound was obtained as yellow solid yellow solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5) R_f = 0.60; (Yield 309 mg (94%) in chloranil); m.p. 200–

201°C; **IR** (neat) 2924, 2853, 1602, 1536, 1470, 1351, 851, 716 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.58 (d, 2H); 8.43–8.37 (m, 4H); 8.25 (d, 2H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ (ppm): 186.5, 172.3, 150.0, 149.3, 137.8, 135.6, 129.5, 128.6, 124.9, 124.3.

2.7.13 3,5-Diphenyl-1,2,4–selenadiazole (4a): The title compound was obtained as a white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5), R_f = 0.65; (Yield 254 mg (89%) in TBN); m.p. 84-85 °C; **IR** (neat) 2852, 1482, 1333, 1240, 965cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.44 (d, 2H), 8.03 (d, 2H), 7.75–7.40 (m, 6H); **^{13}C NMR** (125MHz, $CDCl_3$) δ (ppm): 193.8, 174.4, 134.4, 134.1, 132.1, 130.1, 129.3, 128.8, 128.7, 128.3, 128.2. **HRMS**: Calc. for $C_{14}H_{11}N_2Se$ $[M+H]^+$: 287.0087, Obser: 287.0087.

2.7.14 3,5-Dip-methoxy-1,2,4-selenadiazole (4b): The title compound was obtained as a white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5), R_f = 0.67; (Yield 300 mg (87%) in TBN); m.p. 140 °C; **IR** (neat): 3033, 2942, 1606, 1511, 1485, 1352, 1176, 1152, 1090, 831 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.35 (d, 1H), 7.96 (d, 1H), 7.63–7.58 (m, 2H), 7.04–6.95 (m, 4H), 3.96 (s, 3H), 3.88 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 192.6, 162.8, 133.9, 130.3, 129.9, 119.2, 114.7, 114.5, 113.9, 103.9, 55.5; **HRMS**: Calc. for $C_{16}H_{15}O_2N_2Se$ $[M+H]^+$: 347.0299, Obser: 347.0314.

2.7.15 3,5-Bis (4-fluorophenyl)-1,2,4-selenadiazole (4c): The title compound was obtained as a white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5), R_f = 0.66; (Yield 256 mg (80%) in TBN); m.p. 171–172 ^oC; **IR** (neat): 1640, 1511, 1455, 1409, 1359, 1114, 950, 853cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.40 (dd, 2H), 8.02–7.99 (m, 2H), 7.19 (dt, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 192.4, 173.2, 165.9, 134.6, 130.8, 130.5, 130.4, 116.9, 116.7, 116.6, 116.4, 115.7, 115.5; **HRMS**: Calc. for $C_{14}H_9F_2N_2Se$ $[M+H]^+$: 322.9899, Obser: 322.9916.

2.8 Spectral Data of Synthesized Products

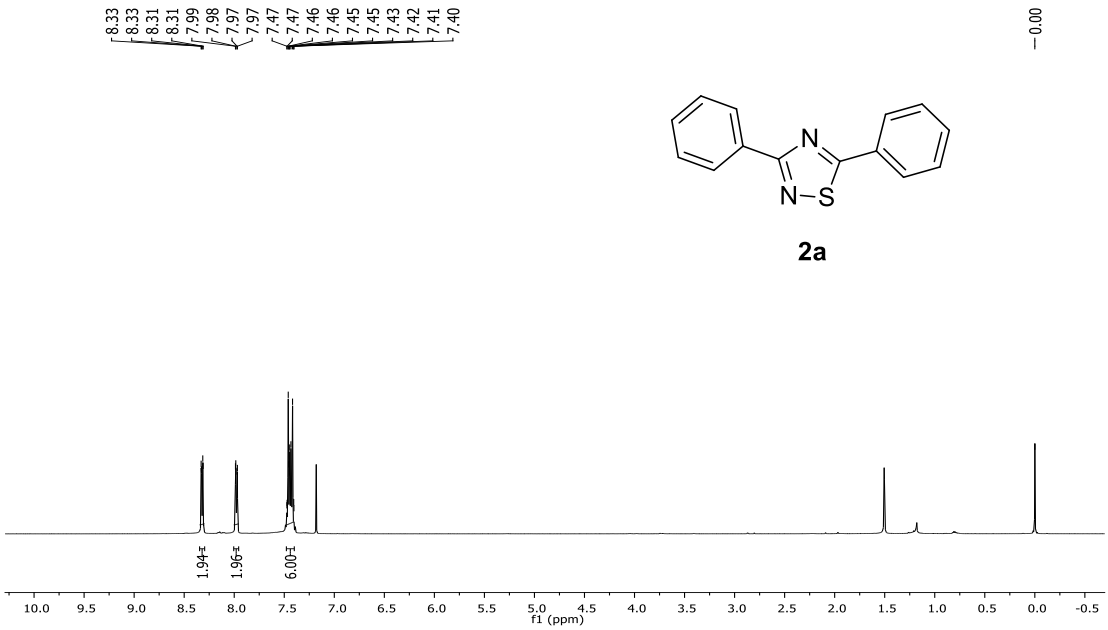


Figure 2.2: ^{1}H NMR of 1,2,4-thiadiazole (**2a**).

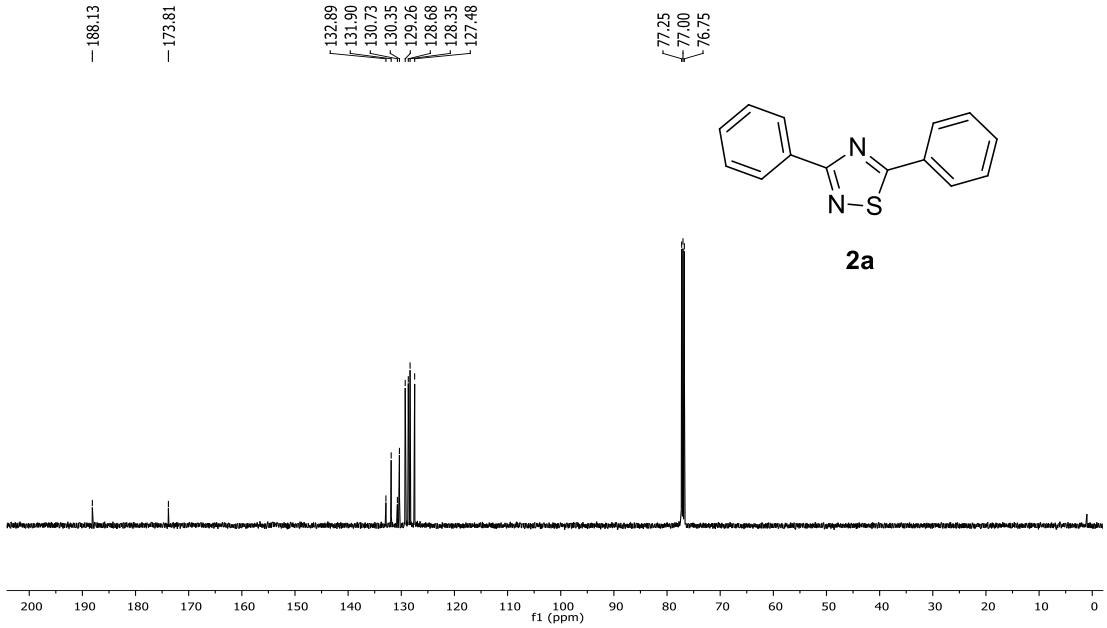


Figure 2.3: ^{13}C NMR of 1,2,4-thiadiazole (**2a**).

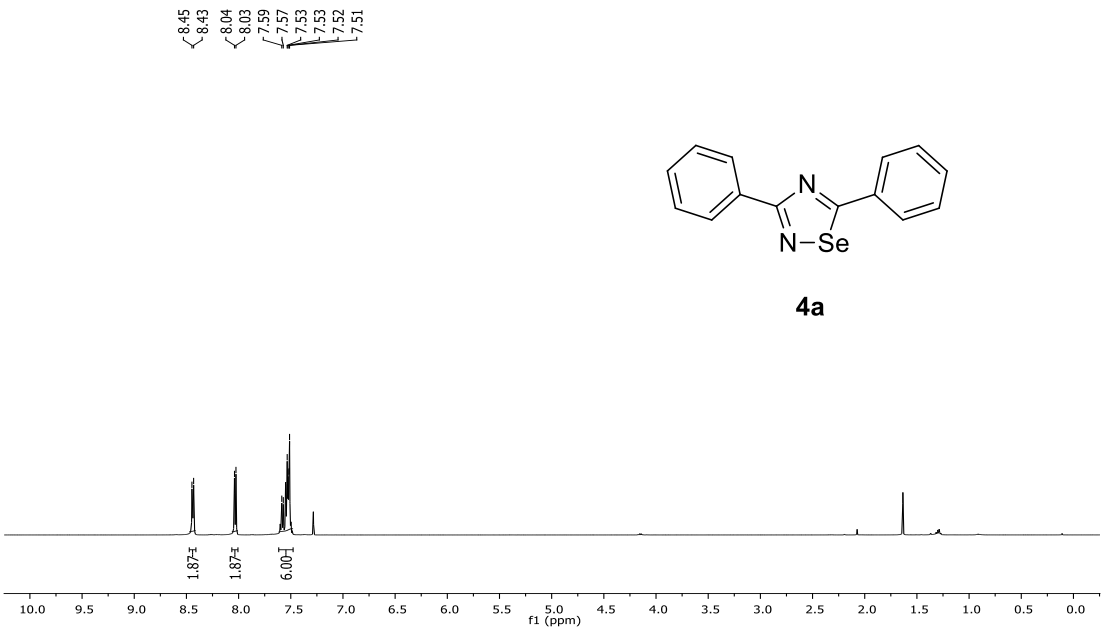


Figure 2.4: ^{1}H NMR of 1,2,4-selenadiazole (**4a**).

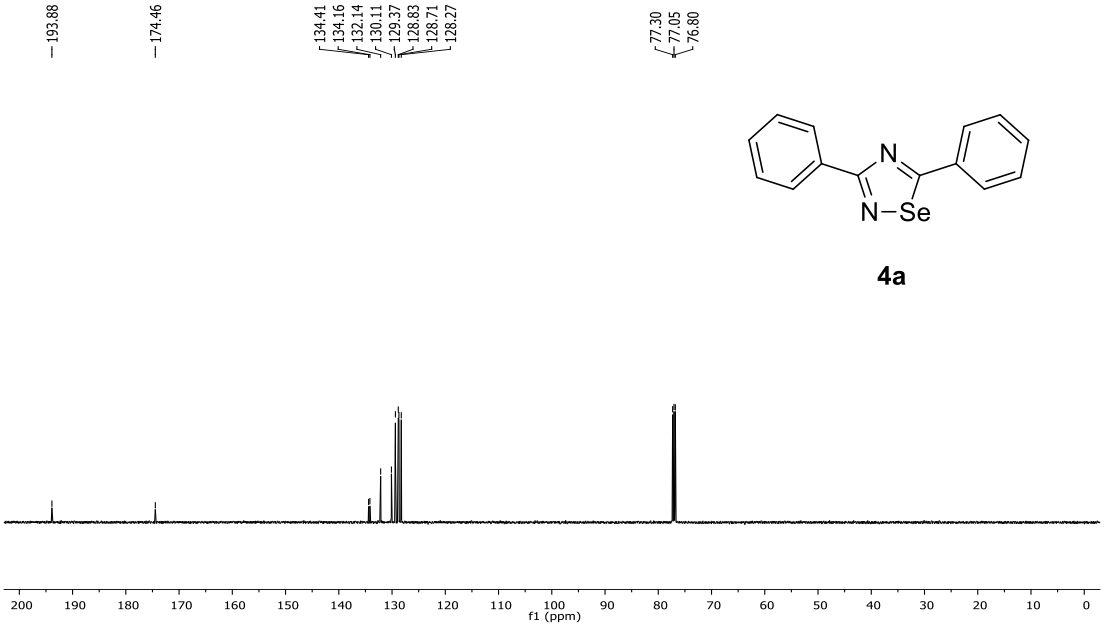


Figure 2.5: ^{13}C NMR of 1,2,4-selenadiazole (**4a**).

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