CHAPTER-V

PART-I

Synthesis of 1,3,4-thiadiazoles Analogues
5.1.1 Introduction

1,3,4-thiadiazoles are important heterocycles with “N–C–S” linkage which can work as the active center, chelate certain metal ions in vivo, and show good tissue permeability. The lower toxicity and in vivo stability of thiadiazole nucleus is attributed to its aromaticity. Thiadiazoles have exhibited potential antiviral, anticancer, antiinflammatory, antibacterial, analgesic, antiglaucoma and fungicidal activities.

Green chemistry has been widely used in the current chemical research to develop efficient, rapid, and eco-friendly synthetic methodologies. The synthesis of organic molecules via solvothermal reaction is of interest because they offer the possibility of environmentally benign reaction conditions by reducing the burden of organic solvent disposal. Recently in our lab Rai et al., have developed the solvothermal method for the synthesis of thioesters and thioamides, isoazoles and pyrazoles, for the conversion of oxadiazoles to thiadiazoles and aldehyde semicarbazones to bishydrazones.

The different synthetic pathways employed to prepare azines proceed rapidly often yield byproducts, which require product separation. In recent years, the study of new protocol that is less hazardous to human health and to the environment has received extensive attention. Therefore, interest in the synthesis of thiadiazole derivatives is significant.
5.1.2 Plan of the Synthesis

A novel, green and efficient method has been developed for the synthesis of 2,5-disubstituted-1,3,4-thiadiazoles under solvothermal conditions in other words closed system at adiabetic condition. This approach exploits the synthetic potential of solvothermal reaction and offers many advantages such as excellent product yields, shorter reaction time, easy isolation of products and eco-friendly benign reaction conditions.

Owing to the potentialities and continuation of our interest in solvothermal reactions, we have developed a novel synthesis of 2,5-disubstituted-1,3,4-thiadiazoles from sulfuration of azines. Usually, semicarbazones were prepared via the reaction of aldehydes or ketones with semicarbazide in the presence of an acid or a base as catalyst.\textsuperscript{16-20} The obtained semicarbazones \textbf{80(a-h)} is heated in an autoclave without solvent for 7-8h at 150-160°C to yield azines \textbf{81(a-h)}. \textbf{Scheme 5.1}

\textbf{Scheme 5.1} Synthesis of azines

Finally the azines \textbf{81(a-h)} were treated with elemental sulphur under solvothermal conditions to get 1,3,4-thiadiazoles as shown in \textbf{Scheme 5.2}.
### Scheme 5.2: Synthesis of 2,5-disubstituted-1,3,4-thiadiazole.

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5.1.3 Discussion on the synthesis of 2,5-disubstituted-1,3,4-thiadiazole

A large number of synthetic methods for the preparation of 1,3,4–thiadiazoles have been reported. The most common procedure involves the cyclization of 1,2–diacylhydrazines or its thia–analogues in presence of SOCl₂ or POCl₃. Symmetrical 2,5–disubstituted–1,3,4–thiadiazoles were synthesized by condensation of various aldehydes, hydrazine and sulfur under microwave irradiation. 1,3,4–thiadiazoles were also synthesized from the corresponding 1,4–dicarbonyl or acyl precursors using P₂S₅ and Lawesson’s reagent, from pentafluorophenyl esters, acid hydrazides and triethylorthoalkanoates and by the oxidation of in situ generated thiosemicarbazones.

The aforementioned methods though provide multitude of choices to contrive substituted 1,3,4–thiadiazoles, suffer from longer reaction time, exhaustive workup, low yield and multistep procedures, which has limited the exploitation of these methods in high throughput synthesis. Thus an improved, efficient, rapid and solvothermal approach to substituted 1,3,4–thiadiazoles is of current interest to organic chemists.

Novel method for the synthesis of azines starting from semicarbazones in an autoclave and their conversion to 2,5–disubstituted–1,3,4–thiadiazole via sulfuration of substituted
azines under solvothermal condition in high yield were as shown in **Scheme 5.1** and **Scheme 5.2** respectively.

The probable mechanism for the formation of 2,5-disubstituted-1,3,4-thiadiazole from azine (a) involves the chelotropic type of cycloaddition. Initially the elemental sulphur attack the azine carbon followed by the cyclisation to yield 2,5-dihydrosubstituted-1,3,4-thiadiazole (b). In intermediate (b) there is addition of two new *sigma* bonds and loss of one *pi* bond which is the criteria for chelotropic reaction. Later the *insitu* generated intermediate (b) undergoes dehydrogenation to yield 2,5-disubstituted-1,3,4-thiadiazole (c). The reason for the dehydrogenation may be attributed to the presence of high temperature and pressure in autoclave reactions and attainment of aromaticity in the final product **Scheme 5.3**.

![Scheme 5.3](image)

**Scheme 5.3:** The possible mechanism for the conversion of azine to 2,5-disubstituted-1,3,4-thiadiazole.
The structural assignments to newly synthesized compounds 81(a–h) and 82(a–h) was based on their elemental analysis and spectral (IR, 1H NMR, 13C NMR and Mass) data. The IR spectra of the compound 81a showed the absence of amide carbonyl absorption band at 1650 cm\(^{-1}\) to 1750 cm\(^{-1}\) and -NH peak at 3400 cm\(^{-1}\) to 3200 cm\(^{-1}\) and showed new peak due to C=N at 1645 cm\(^{-1}\). In the 1H NMR spectra the signals of the newly synthesized compounds were verified on the basis of their chemical shifts, multiplicities, and coupling constants. The formation of compound 81a was confirmed by the disappearance of peak at \(\delta\) 6.7 and 7.9 due to -NH and -NH\(_2\). In 13C NMR spectra, appearance of a doublet at \(\delta\) 161.0 ppm due to C=N substantiated the formation of compound 81a.

The IR spectra of the compound 82a showed the appearance of a new peak at 670 cm\(^{-1}\) due to C-S stretching. The IR spectra of all other synthesized compounds showed characteristic signals at 1642-1651 cm\(^{-1}\) for (C=N) and 1570-1460 cm\(^{-1}\) for (C=C). In 1H NMR spectra, disappearance of peak at \(\delta\) 8.9 due to –CH=N and in 13C NMR appearance of peaks at \(\delta\) 174.1 ppm due to C-S linkage confirms the formation of cyclised heterocycle 82a. The aryl moiety exhibited characteristic signals in the aromatic region of the spectrum. The mass spectrum of all the compounds showed molecular ion peak at M\(^+\) or M+1 corresponding to its molecular formula, which confirmed its chemical structure.
5.1.4 Experimental results for the synthesis of 2,5-disubstituted-1,3,4-thiadiazole.

General

All chemicals were obtained from commercial suppliers and used without further purification. Melting points were determined in open capillaries on a Buchi oil melting point apparatus and are uncorrected. Reactions were monitored by using TLC on aluminum sheets precoated with silica gel 60 F254 (0.2 mm, Merck). For column chromatography, silica gel of 100-200 mesh size was used. 1H NMR spectra were acquired on Agilent-NMR-vnmrs 400 MHz instrument in DMSO- d6 or CDCl3. 13C NMR spectra were recorded on a Bruker AMX-400 (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent as the internal reference (CDCl3: δ 77.0 ppm or DMSO δ 40.0 ppm). Mass spectrometry was performed with a Bruker-Franzen Esquire LC mass spectrometer unless otherwise stated.

General Procedure for the synthesis of bishydrazone (1E, 2E)-1,2-dibenzylidenehydrazine (81a):

(E)-2-benzylidenehydrazinecarboxamide (80a, 1g, 6.13 mmol) was taken in a autoclave reaction container (Teflon Liner). The lid was placed and was lowered into the autoclave, the plates were kept over it and the autoclave was closed and tightened. It was kept in the oven at 150-170°C for 7-8hr. The products after cooling, were extracted into
diethyl ether (20 mL), washed thoroughly with water. TLC of the solution shows single spot, which was different from the starting material. The organic layer was dried over anhydrous Na$_2$SO$_4$, solvent was evaporated under reduced pressure and the product obtained as yellow crystalline solid in 90% yield (1.15 g), mp 89-92°C (lit 88-89°C). IR cm$^{-1}$ (Nujol): 1645 cm$^{-1}$ (C=N); $^1$H NMR (400 MHz, CDCl$_3$), $\delta$ ppm (J, Hz): 7.48-7.54 (m, 6H), 7.88-7.91 (d, 4H, $J$ = 7.2), 8.72 (s, 2H); $^{13}$C NMR (100MHz CDCl$_3$): $\delta$ (ppm) 129.1, 129.7, 132.4, 137.3, 161.0; MS (relative intensity): m/z for C$_{14}$H$_{12}$N$_2$: 209.2 [M+H]$^+$ (100) Anal. % Calc: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.68; H, 5.85; N, 13.49.

The same procedure was followed in all the case.

**Synthesis of (1E, 2E)-1,2-bis(4-methoxybenzylidene)hydrazine (81b):**

![81b](image)

Obtained from (E)-2-(4-methoxybenzylidene)hydrazine carboxamide (80b, 1g, 5.18mmol) as a yellow crystalline solid in 92% yield (1.28 g), mp 166-168°C (lit 166-169°C). IR cm$^{-1}$ (Nujol): 1649 cm$^{-1}$ (C=N); $^1$H NMR (400 MHz, CDCl$_3$), $\delta$ ppm (J, Hz): 3.86 (s, 6H), 6.96-6.97 (d, 4H, $J$ = 8.8 ), 7.78-7.79 (d, 4H, $J$ = 8.8), 8.62 (s, 2H); $^{13}$C NMR (100MHz CDCl$_3$): $\delta$ (ppm) 55.3, 55.4, 114.2, 126.9, 130.1, 161.0, 161.9; MS (relative intensity): m/z for C$_{16}$H$_{16}$N$_2$O$_2$: 269.3 [M+H]$^+$; Anal. % Calc: C, 71.62; H, 6.01; N, 10.44; Found: C, 71.60; 6.03; N, 10.45.
Synthesis of 4,4′-(1E,1′E)-hydrazine-1,2-diylidenebis(methanylylidene)bis(N,N-dimethylaniline) (81c):

Obtained from (E)-2-(4-(dimethylamino)benzylidene)hydrazinecarboxamide (80c, 1g, 4.85 mmol) as a yellow crystalline solid in 90% yield (1.28 g), mp 253-254°C (250-253°C). IR cm⁻¹ (KBr): 1650 cm⁻¹ (C=N); ¹H NMR (400 MHz, CDCl₃): δ (ppm) 3.03 (s, 12H), 6.77-6.75 (d, 4H, J = 8.8), 7.87-7.89 (d, 4H, J = 8.8), 8.50 (s, 2H); ¹³C NMR (100MHz CDCl₃): δ (ppm) 40.2, 111.9, 118.4, 128.7, 151.8, 160.1; MS (relative intensity): m/z for C₁₈H₂₂N₄; 295.4 [M+H]⁺ (100); Anal. % Calc: C, 73.44; H, 7.53; N, 19.03. Found: C, 73.50; H, 7.50; N, 19.00.

Synthesis of (1E, 2E) - 1,2-bis (4-chlorobenzylidene) hydrazine (81d):

Obtained from (E)-2-(4-chlorobenzylidene)hydrazinecarboxamide (80d, 1g, 5.06 mmol) as yellow crystalline solid in 93% yield 1.30g), mp 207-209°C (208-210°C). IR (Nujol): 1640 cm⁻¹ (C=N); ¹H NMR (400 MHz, CDCl₃), δ ppm (J, Hz): 7.40-7.43 (d, 4H, J = 8.8), 7.75-7.78 (d, 4H, J = 8.8), 8.60 (s, 2H); ¹³C NMR (100MHz CDCl₃): δ (ppm) 129.1, 129.7, 132.5, 137.3, 161.0. MS (relative intensity): m/z for C₁₄H₁₀Cl₂N₂; 276.1 [M⁺] (100), 278.1
Synthesis of (1E, 2E)-1,2-bis(2-chlorobenzylidene)hydrazine (81e):

Obtained from (E)-2-(2-chlorobenzylidene)hydrazinecarboxamide (80e, 1g, 5.06 mmol) as a yellow crystalline solid in 89% yield (1.25 g), mp 142-144°C. IR cm\(^{-1}\) (Nujol): 1638 cm\(^{-1}\) (C=N); \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) ppm (J, Hz): 7.32-7.45 (m, 6H), 8.21-8.23 (d, 4H, J = 6.0), 9.09 (s, 2H); \(^{13}\)C NMR (100MHz CDCl\(_3\)): \(\delta\) (ppm) 127.0, 128.3, 130.0, 131.4, 132.2, 133.6, 135.8, 159.0; MS (relative intensity): m/z for C\(_{14}\)H\(_{10}\)Cl\(_2\)N\(_2\); 276.1 [M+] (100), 278.1 [M+2], 280.1 [M+4]; Anal. % Calc: C, 60.67; H, 3.64; N, 10.11. Found: C, 60.66; H, 3.64; N, 10.12.

Synthesis of (1E,2E)-1,2-bis(3-nitrobenzylidene)hydrazine (81f):

Obtained from (E)-2-(4-nitrobenzylidene)hydrazinecarboxamide (80f, 1g, 4.80 mmol) as a yellow crystalline solid in 95% yield (1.36 g), mp 190-193°C (lit 195-196°C). \(^{29}\) IR cm\(^{-1}\) (Nujol): 1640 cm\(^{-1}\) (C=N); \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) ppm (J, Hz): 7.75-7.77 (d, 2H, J = 8.8), 7.95-7.97 (d, 2H, J = 8.8), 8.13-8.15 (d, 2H, J = 8.8), 8.45 (s, 2H), 8.62 (s, 2H); \(^{13}\)C NMR (100MHz CDCl\(_3\)): \(\delta\) (ppm) 124.2, 126.0, 129.8, 133.9, 135.9, 148.0, 161.2; MS (relative intensity): m/z for C\(_{14}\)H\(_{10}\)N\(_4\)O\(_4\); 299.2
Synthesis of 1,3,4-thiadiazoles

[Synthesis of (1E, 2E)-1,2-bis(4-nitrobenzylidene)hydrazine (81g):

81g

Obtained from (E)-2-(3-nitrobenzylidene)hydrazinecarboxamide (80g, 1g, 4.80 mmol) as a yellow crystalline solid in 93% yield (1.33g), mp 297-299°C (299-302°C). IR cm\(^{-1}\) (Nujol): 1642 cm\(^{-1}\) (C=N); \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) ppm (J, Hz): 6.93-6.96 (d, 4H, J = 8.8), 7.75-7.78 (d, 4H, J = 8.8), 8.60 (s, 2H); \(^13\)C (100 MHz; CDCl\(_3\)): \(\delta\) ppm 114.2, 126.9, 130.1, 161.1, 161.9; MS (relative intensity): m/z for C\(_{14}\)H\(_{10}\)N\(_4\)O\(_4\); 299.2 [M+H]\(^+\) (100); Anal. % Calc: C, 56.38; H, 3.38; N, 18.78; Found: C, 56.36; H, 3.41; N, 18.77.

Synthesis of (1E, 2E)-1,2-bis(3,4,5-trimethoxybenzylidene)hydrazine (81h):

81h

Obtained from (E)-2-(3,4,5-trimethoxybenzylidene)hydrazinecarboxamide (80h, 1g, 3.95mmol) as a yellow crystalline solid in 90% yield (1.38g), mp 191-193°C (lit 190-192). IR cm\(^{-1}\)(Nujol) 1649 cm\(^{-1}\) (C=N); \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) ppm (J, Hz): 3.90 (s, 12H), 3.95 (s, 6H), 7.09-7.11 (d, 4H, J = 8.8), 8.57 (s, 2H); \(^13\)C NMR (100MHz CDCl\(_3\)): \(\delta\) (ppm) 56.1, 56.2, 60.9, 105.5, 129.4, 140.8, 153.4,
160.5; MS (relative intensity): m/z for C$_{20}$H$_{24}$N$_2$O$_6$: 389.4 [M+H]$^+$ (100); Anal. % Calc: C, 61.84; H, 6.23; N, 7.21; Found: C, 61.83; H, 6.22; N, 7.23.

**General Procedure for the Synthesis of 2,5-disubstituted-1,3,4-thiadiazole (82a):**

(1E, 2E)-1,2-dibenzylidenehydrazine (81a, 1g, 4.80 mmol) and sulphur (0.08g, 2.40 mmol) was taken in an autoclave reaction container (Teflon Liner). The lid was placed and was lowered into the autoclave, the plates were kept over it and the autoclave was closed and tightened. It was kept in the oven at 150°-170°C for 6-7hr. The products obtained after cooling, were extracted into diethyl ether (20mL), washed thoroughly with water. TLC of the solution shows single spot, which was different from the starting material. The organic layer was dried over anhydrous sodium sulphate; solvent was evaporated under reduced pressure and the product obtained as yellow crystalline solid in 90% yield (1.03g). mp 158-161°C. IR cm$^{-1}$ (Nujol): 1648 cm$^{-1}$ (C=N) and 670 cm$^{-1}$ (C=S); $^1$H NMR (400 MHz, CDCl$_3$). $\delta$ ppm (J, Hz): 7.50-7.56 (m, 6H), 7.89-7.95 (d, 4H, $J = 8.8$) (Figure 5.1); $^{13}$C NMR (100 MHz CDCl$_3$). $\delta$ (ppm) 128.7, 129.2, 130.9, 133.5, 174.1 (Figure 5.2); MS (relative intensity): m/z for C$_{14}$H$_{10}$N$_2$S: 238.9 [M+H]$^+$ (100) (Figure 5.3); Anal. % Calc: C, 70.56; H, 4.23; N, 11.76; Found: C, 70.53; H, 4.25; N, 11.77.
The same procedure was followed in all the cases.

**Synthesis of 2,5-bis(4-methoxyphenyl)-1,3,4-thiadiazole (82b):**

![Structure of 82b]

Obtained from (1E, 2E)-1,2-bis(4-methoxybenzylidene)hydrazine (81b, 1g, 3.73 mmol) and sulphur (0.06g, 1.86 mmol) as a yellow crystalline solid in 92% yield (1.02g), mp 195-198°C. IR cm⁻¹ (Nujol): 1650 cm⁻¹ (C=N), 672 cm⁻¹ (C-S); ¹H NMR (400 MHz, CDCl₃), δ ppm (J, Hz): 3.88 (s, 6H), 6.98-7.00 (d, 4H, J = 8.8), 7.92-7.94 (d, 4H, J = 8.8); ¹³C NMR (100MHz CDCl₃): δ (ppm) 55.4, 55.5, 114.5, 123.0, 129.3, 161.7; MS (relative intensity): m/z for C₁₆H₁₄N₂O₂S: 298.9 [M+H]⁺ (100); Anal. % Calc: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.37; H, 4.78; N, 9.38.

**Synthesis of 4,4’-(1,3,4-thiadiazole-2,5-diyl)bis(N,N-dimethylaniline) (82c):**

![Structure of 82c]

Obtained from 4,4’-((1E, 1’E)-hydrazine-1,2-diyldenedibis(methanylylidene))bis(N,N-dimethylaniline) (81c, 1g, 3.40 mmol) and sulphur (0.05g, 1.70 mmol) as a yellow crystalline solid in 95% yield (1.05g), mp 89-90°C. IR cm⁻¹ (Nujol): 1651 cm⁻¹ (C=N), 675 cm⁻¹ (C-S); ¹H NMR (400 MHz, CDCl₃), δ ppm (J, Hz): 3.03 (s, 12H), 6.72-6.74 (d, 4H, J = 8.8), 7.83-7.85 (d, 4H, J = 8.8); ¹³C NMR (100MHz CDCl₃): δ (ppm) 40.1, 111.8, 118.3, 128.9, 151.8, 166.8; MS (relative intensity):
m/z for $\text{C}_{18}\text{H}_{20}\text{N}_{4}\text{S}$: 325.0 [M+H]$^+$ (100); Anal. % Calc: C, 66.63; H, 6.21; N, 17.27. Found: C, 66.60; H, 6.22; N, 17.29.

**Synthesis of 2,5-bis(4-chlorophenyl)-1,3,4-thiadiazole (82d):**

![Diagram](image)

Obtained from $(1E, 2E)$-1,2-bis(4-chlorobenzylidene)hydrazine (81d, 1g, 3.61 mmol) and sulphur (0.06g, 1.80mmol) as a yellow crystalline solid in 91% yield (1.00g), mp, 193-195°C. IR cm$^{-1}$ (Nujol): 1643 cm$^{-1}$ (C=N) and 670 cm$^{-1}$ (C-S); $^1$H NMR (400 MHz, CDCl$_3$), $\delta$ ppm (J, Hz): 7.57-7.59 (d, 4H, J = 8.0), 7.89-7.91 (d, 4H, J = 8.0); $^{13}$C NMR (100MHz CDCl$_3$): $\delta$ (ppm) 128.7, 128.9, 131.3, 134.3, 162.6; MS (relative intensity): m/z for $\text{C}_{14}\text{H}_{8}\text{Cl}_{2}\text{N}_{2}\text{S}$: 306.8 [M+] (100), 308.8 [M+2], 311.8 [M+3]; Anal. % Calc: C, 54.74; H, 2.62; N, 9.12. Found: C, 54.77; H, 2.58; N, 9.15.

**Synthesis of 2,5-bis(2-chlorophenyl)-1,3,4-thiadiazole (83e):**

![Diagram](image)

Obtained from $(1E, 2E)$-1,2-bis(2-chlorobenzylidene)hydrazine (82e, 1g, 3.61mmol) and sulphur (0.06g, 1.80mmol) as yellow crystalline solid in 89% yield (0.98g), mp 189-192°C. IR cm$^{-1}$ (Nujol): 1642 cm$^{-1}$ (C=N) and 680 cm$^{-1}$ (C-S); $^1$H NMR (400 MHz, CDCl$_3$), $\delta$ ppm (J, Hz): 7.21-7.25 (m, 2H), 7.39-7.43 (m, 4H), 8.07-8.08 (m, 2H); $^{13}$C NMR (100MHz CDCl$_3$): $\delta$ (ppm) 127.3, 129.2, 129.5, 130.3, 132.4, 137.1, 174.1; MS (relative intensity) m/z for $\text{C}_{14}\text{H}_{8}\text{Cl}_{2}\text{N}_{2}\text{S}$: 306.8 [M+]
(100), 308.8 [M+2], 311.8 [M+3]; Anal. % Calc: C, 54.74; H, 2.62; N, 9.12. Found: C, 54.78; H, 2.59; N, 9.13.

**Synthesis of 2,5-bis(3-nitrophenyl)-1,3,4-thiadiazole (82f):**

\[
\begin{align*}
\text{82f} & \quad \text{Obtained from (1E, 2E)-1,2-bis(3-nitrobenzylidene)hydrazine}\quad (81f, 1g, 3.35\text{mmol}) \text{ and sulphur (0.05g, 1.67mmol) as yellow crystalline solid in 85% yield (0.93g, mp 201-203°C. IR cm}^{-1}\text{ (Nujol): 1645 cm}^{-1}\text{ (C=N) and 670 cm}^{-1}\text{ (C-S); }^1\text{H NMR (400 MHz, CDCl}_3\text{), }\delta \text{ ppm (}J, \text{Hz): 7.84-7.87 (d, 2H, } J = 8.8), 7.99-8.02 (d, 2H, } J = 8.8), 8.21-8.23 (d, 2H, } J = 8.8), 8.45 (s, 2H); ^{13}\text{C NMR (100MHz CDCl}_3\text{): } \delta \text{ (ppm) 128.1, 128.9, 131.3, 134.5, 162.7; MS (relative intensity) m/z for } C_{14}H_8N_4O_4S: 329.0 [M+H]^+ \text{ (100); Anal. % Calc: C, 51.22; H, 2.46; N, 17.07 Found: C, 51.15; H, 2.52; N, 17.08.} 
\end{align*}
\]

**Synthesis of 2,5-bis(4-nitrophenyl)-1,3,4-thiadiazole (82g):**

\[
\begin{align*}
\text{82g} & \quad \text{Obtained from (1E, 2E)-1,2-bis(4-nitrobenzylidene)hydrazine}\quad (81g, 1g, 3.35\text{mmol}) \text{ and sulphur (0.05g, 1.67mmol) as a yellow crystalline solid in 91% yield (1.00g, mp 210-214°C. IR cm}^{-1}\text{ (Nujol): 1649 cm}^{-1}\text{ (C=N) and 675 cm}^{-1}\text{ (C-S); }^1\text{H NMR (400 MHz, CDCl}_3\text{), }\delta \text{ ppm (}J, \text{Hz): 6.99-7.01 (d, 4H, } J = 8.8), 7.93-7.94 (d, 4H, } J = 8.8); ^{13}\text{C NMR (100MHz CDCl}_3\text{): } \delta \text{ (ppm) 114.5, 123.0, 129.3, 161.7; MS (relative intensity) m/z for } C_{14}H_8N_4O_4S: 329.0
\end{align*}
\]
[M+H]$^+$ (100); Anal. % Calc: C, 51.22; H, 2.46; N, 17.07 Found: C, 51.16; H, 2.51; N, 17.08.

**Synthesis of 2,5-bis(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazole**

(82h):

Obtained from (1E, 2E)-1,2-bis(3,4,5-trimethoxybenzylidene)hydrazine (81h, 1g, 2.57mmol) and sulphur (0.04g, 1.28mmol) as yellow crystalline solid in 85% yield (0.96g), mp 237-240°C. IR cm$^{-1}$ (Nujol): 1645 cm$^{-1}$ (C=N) and 670 cm$^{-1}$ (C-S); $^1$H NMR (400 MHz, CDCl$_3$), $\delta$ ppm ($J$, Hz): 3.90 (s, 6H), 3.99 (s, 12H), 7.13-7.15 (d, 4H, $J$ = 8.8); $^{13}$C NMR (100MHz CDCl$_3$): $\delta$ (ppm) 56.1, 57.2, 60.9, 129.4, 140.8, 153.5, 161.5; MS (relative intensity) m/z for C$_{20}$H$_{22}$N$_2$O$_6$S: 419.0 [M+H]$^+$ (100); Anal. % Calc: C, 57.40; H, 5.30; N, 6.69. Found: C, 57.35; H, 5.32; N, 6.72.
Figure 5.1: $^1$HNMR Spectrum of compound 82a
Figure 5.2: $^{13}$C NMR Spectrum of compound 82a
Figure 5.3: $^1$HNMR Spectrum of compound 82a
5.2.1 Reference:


