Microwave, Ultrasound mediated and conventional method of syntheses of some thiosemicarbazides and thia diazoles
SECTION A:
Formation of thiosemicarbazides with the reaction of acid hydrazide and aryl
isothiocyanate in ethanol to give N-aryl-2-[(2,3,4,6-tetrafluoro-phenoxy)-acetyl]-
hydrazine carbothioamide

3.1.1 Introduction and Literature search
During the recent years there has been intense investigation of different classes of
thiosemicarbazide compounds, many of which are known to possess interesting
biological properties such as antibacterial,\(^1\) antifungal,\(^2\) anticonvulsant,\(^3\) antimicrobial
\(^4\)and antitumor agents.\(^5\) Thiosemicarbazides are valuable blocks for the syntheses of
five–membered heterocycles.\(^6\) Published syntheses of thiosemicarbazides \(1\)
(Scheme 3.1.1) include (i) reactions of isothiocyanates with hydrazines, the method
most frequently used,\(^7a-c\) (ii) reduction of thiosemicarbazones by sodium borohydride
is used for the preparation of and only applicable if \(R^2 = H\), mono-, di-, and tri–
substituted \(1\) (but not tetra- or pentasubstituted);\(^8\) (iii) reactions of hydrazines with
reactive thiocarbamic acid derivatives; the yields (66-73\%) were affected by side
reactions,\(^9\text{–}11\) (iv) reactions of cyanohydrazines with hydrogen sulfide can yield mono
or disubstituted thiosemicarbazides \(1\) (\(R^1=R^2=H\));\(^12\) and (v) reactions of
1,2,4–triazolyl or bis(imidazolyl)methanethiones with amines then with hydrazines to
give di– and trisubstituted thiosemicarbazides \(1\).\(^13,14\)
Recently, was reported an efficient syntheses of thiosemicarbazide\textsuperscript{15} (\textbf{Scheme 3.1.2}) from
a) benzonitriles,\textsuperscript{16} b) reaction of 4–nitrophenyloxyacetyl chloride with ammonium
thiocyanate using PEG–400 as PTC under 600 watt MW irradiation for 9 minutes to
give aryl thiocyanate, which \textit{in situ} on reaction with aryl hydrazide under 675 watt MW
irradiation for 4 minutes gives thiosemicarbazide (\textbf{Scheme 3.1.3})
Green chemistry is widely adopted to meet the fundamental scientific challenges of protecting the human health and environment and also achieving commercial viability since the chemical and pharmaceutical industries are always under pressure to develop more environmentally friendly organic reaction methodologies, therefore the emerging area of green chemistry envisages minimum hazard as the performance criteria while designing new chemical process. The target is to explore alternative reaction conditions and media to get the desired chemical transformations with minimum by products or waste generation as well as to eliminate the use of organic solvents. Over the past few decades ultrasound and microwave (MW) irradiation have attracted attention for efficient and relatively friendlier syntheses of a variety of organic compounds. The energy (0.0016 eV) of microwave photon in all domestic “kitchen” MW ovens and dedicated MW reactors for chemical syntheses operating at a frequency of 2.45 GHz (wavelength of 12.24 cm) is too low to break chemical bonds and is clear that MW cannot induce chemical reaction. Thus MW assisted chemical reactions occur only due to efficient heating by “MW dielectric heating.” The use of domestic MW oven as a source of energy in organic syntheses is now well established. Use of MW for rapid heating results reduction in the reaction period. MW–mediated protocols have been widely applied to the formation of a variety of Carbon–heteroatom and Carbon–Carbon bonds.
A) Formation of Carbon–nitrogen bond.\textsuperscript{22}

\[
\begin{align*}
\text{OH} & \quad \text{EtOH, reflux 24-36h} \\
& \quad \text{or EtOH, MW 150 °C} \\
& \quad \text{20-30 min}
\end{align*}
\]

B) Direct amination of aryl halide without transition metal catalyst.\textsuperscript{23}

\[
\begin{align*}
\text{KOH } \text{Bu, DMSO} \quad \text{MW} \\
\end{align*}
\]

Sonochemistry is a subject in which sound energy is used to affect chemical processes in which non electromagnetic radiation accelerates and executes chemical reaction. The phenomenon of cavitation (formation and behavior of gas or vapor bubbles and bubble clouds in a liquid) is the origin of Sonochemical effect and the physical phenomenon like high temperatures or electrical fields, during cavitation result in cleavage of bonds\textsuperscript{24} therefore organic syntheses via ultrasound is a preferential domain of radicals, radical ions and single electron transfers (SET).

i) Refomtmsky reaction\textsuperscript{25}

\[
\begin{align*}
\text{N} & \quad \text{Me} \\
\text{Br} & \quad \text{Zn (Ag), THF} \\
& \quad \text{40 °C, )}, 2h
\end{align*}
\]

ii) Diels–Alder reaction\textsuperscript{26}
iii) Rearrangement reaction\textsuperscript{27}

3.1.2 Present Work

This section reveals the syntheses of thiosemicarbazides using acid hydrazide and aryl isothiocyanate in ethanol to give N–aryl–2–[(2,3,4,6-tetrafluoro–phenoxy)–acetyl]–hydrazine carbothioamide.

(Scheme 3.1.4)
3.1.3 Results and Discussion

All the recorded melting points were determined in open capillary tubes and are uncorrected. IR. spectra were recorded on Perkin–Elmer FT–IR spectrophotometer in KBr disc. Purity of the compounds was checked by TLC on silica gel G plates.

**Table 3.1.1:** Characterization data of N-aryl–2–[(2,3,4,6-tetrafluoro-phenoxy)–acyl]–hydrazine carbothioamide

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Compd</th>
<th>Ar</th>
<th>M.P (°C)</th>
<th>Ultrasound</th>
<th>Microwave</th>
<th>Conventional</th>
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<td></td>
<td></td>
<td>Time (min)</td>
<td>Yield (%)</td>
<td>Time (min)</td>
</tr>
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<tr>
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<tr>
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<td>phenyl</td>
<td>168</td>
<td>20</td>
<td>73</td>
<td>3.0</td>
</tr>
</tbody>
</table>

$\gamma_{\text{max}}$ (KBr disk / cm$^{-1}$) (14a): 3365, 3241, 2939, 1692, 1515, 1203.

$\gamma_{\text{max}}$ (KBr disk / cm$^{-1}$) (14d): 3276, 3238, 2927, 1708, 1518, 1197.

3.1.4 Experimental

**Method [A]:** (conventional method) : Equimolar amount (0.01 mole) of acid hydrazide 13 and aryl isothiocyanates was dissolved in ethanol (12–15mL) and refluxed for 50 minutes. The reaction was monitored by TLC. On completion, the solid that precipitated was filtered and recrystallized from ethanol to give 14. This typical experimental procedure was followed to prepare other analogs of this series.
Compounds 14a-e were synthesized by the above general procedure and listed in Table 3.1.1 with their characterization data. The structures are confirmed by IR spectra.

**Method [B]: (ultrasound method):** Equimolar amount (0.01 mole) of acid hydrazide 13 and aryl isothiocyanates was dissolved in ethanol (12–15mL) and the reaction mixture was subjected for ultrasound irradiation for 25 minutes. Progress of reaction was monitored by TLC. The precipitated solid was filtered and recrystallized from ethanol to give 14. This typical experimental procedure was followed to prepare other analogs of this series.

Compounds 14a-e were synthesized by the above general procedure and listed in Table 3.1.1 with their characterization data.

**Method [C]: (MW method):** Equimolar amount (0.01 mole) of acid hydrazide 13 and aryl isothiocyanates when dissolved in ethanol (12–15mL) was irradiated in a borosilicate glass beaker (50 mL) inside a MW oven for 60 seconds. at an output of 300 watts power, with short interruption of 15 seconds to avoid excessive evaporation of solvent. Progress of reaction was monitored by TLC. The reaction mixture was cooled and poured over crushed ice containing water. Solid that separated was filtered and recrystallized with ethanol to give 14. This typical experimental procedure was followed to prepare other analogs of this series.

Compounds 14a-e were synthesized by the above general procedure and listed in Table 3.1.1 with their characterization data.

### 3.1.5 References

PART III

SECTION B:
Syntheses of 2–[(2,4–difluoro–6–iodophenyl)–carbonyl]–N–arylhydrazine
carbothioamide in ethanol

3.2.1 Introduction and Literature search
In this section we shall focus on chemistry and synthetic application of thiosemicarbazides which are represented by 26, and may exist alternatively in, or in tautomeric equilibrium with the zwitterionic form 27.

![Diagram]

Its chemistry deals with reactions promoted by nucleophilic reactivity of these compounds, the center of reaction being located either at the sulfur or nitrogen atom.

a) Formation of S–alkyl derivative on treatment with alkyl halides.\textsuperscript{1,2}

![Diagram]

b) Formation of thiosemicarbazone.\textsuperscript{3}

\[
\text{H}_2\text{N-CS-NH-NH}_2 + \text{X} - \text{CHR}_2\beta \text{Me} \rightarrow \text{H}_2\text{N-CS-NH-N=CR}_2\beta \text{Me}
\]

Under neutral condition (Scheme 3.2.1) 1–acylthiosemicarbazides 2 may undergo ring–closure to yield a mixture of 3 and 4, whereas under specified conditions either 3 or 4
may be obtained specifically.\textsuperscript{4,5} 1–Substituted thiosemicarbazides 5 that are unsubstituted at the 4–position are acylated at that position and under the conditions of ring–closure yieldd compound 6.\textsuperscript{4} 1,4–Disubstituted thiosemicarbazides 7 react with acylating agents to form meso–ionic compounds 8.\textsuperscript{4}

\[
\begin{align*}
\text{HN–NHR}^4 \quad & \xrightarrow{i} \quad \text{HN–NHR}^4 \\
\text{SC–NH}_2 & \quad \xrightarrow{i} \quad \text{SC–NH}_2
\end{align*}
\]

\[
\begin{align*}
\xrightarrow{\text{OH}^–, \text{H}_2\text{O}} & \quad \xrightarrow{\text{OH}^–, \text{H}_2\text{O}} \\
\quad & \quad \xrightarrow{\text{OH}^–, \text{H}_2\text{O}}
\end{align*}
\]

\[
\begin{align*}
\text{HN–NHR}^4 & \quad \xrightarrow{i} \quad \text{HN–NHR}^4 \\
\text{SC–NHR}^2 & \quad \xrightarrow{i} \quad \text{SC–NHR}^2
\end{align*}
\]

\[
\begin{align*}
\xrightarrow{\text{OH}^–, \text{H}_2\text{O}} & \quad \xrightarrow{\text{OH}^–, \text{H}_2\text{O}} \\
\quad & \quad \xrightarrow{\text{OH}^–, \text{H}_2\text{O}}
\end{align*}
\]

\[
\begin{align*}
i : & \quad \text{R}^3\text{COCl}, (\text{R}^3\text{CO})_2\text{O}, \text{R}^3\text{CO}_2\text{H}, \text{R}^3\text{CO}_2\text{R} \quad \text{or} \quad \text{R}^3\text{C}({\text{OR}})_3
\end{align*}
\]

Scheme 3.2.1

Thiosemicarbazides, unsubstituted in the 1–position form six–membered heterocyclic compounds in reaction with \( \alpha \)–diketones, acyloins, and \( \alpha \)–oxo esters.\textsuperscript{4}
Synthetic application of thiosemicarbazide:—Thiosemicarbazides are easily cyclized by acids, bases or oxidants therefore they are versatile building blocks for the preparation of heterocyclic rings. For example thiazoles, thiazines, thiadiazoles, thiazadiazines, pyrazines, indazoles

a) Syntheses of 1,2,4-triazole.

b) Reaction of Thiosemicarbazide and 5–Halovalerenones.
Thiosemicarbazide with ferrocenyl (Fc) substituted α,β-enones give dihydro pyrazoles.\textsuperscript{10}

\[ \text{R}^1 = \text{Fc}; \text{R}^2 = \text{Ph}, \text{p-C}_6\text{H}_4\text{OMe}, \text{C}_6\text{H}_4\text{Br}, \text{Fc} \]

c) Syntheses of Pyrazinethiones.\textsuperscript{11}
d) Reaction of thiosemicarbazide with 1,3-Dibromopropyne to give triazine.\textsuperscript{12}

In this section we shall see different types MW assisted organic reactions.

a) Heck reaction:—Intramolecular MW assisted Heck cyclization using Pd(OAc)\textsubscript{2}/PPh\textsubscript{3} gives seven membered N–heterocycle.\textsuperscript{13}

b) Heterocycle Syntheses:—Formation of different heterocycle rings by cycloaddition reaction are well suited for MW technology as they require high temperature for many hours or even days.
i) Molteni et al. have described the syntheses of pyraoles. \(^{14}\)

\[
\begin{align*}
\text{O} & + \text{MeO} \begin{array}{c}
\text{N} \\
\text{Me}\end{array} + R-\text{NH}-\text{NH}_2 \xrightarrow{\text{H}_2\text{O}, 2.6 \text{ equiv AcOH}} \text{MW, 220 °C} \\
\text{1 min (15-18 bar)} \\
\end{align*}
\]

\[
\begin{array}{c}
\text{O} \\
\text{N}\end{array}
\]

ii) Bohlmann–Rahtz syntheses of trisubstituted pyridines. \(^{15}\)

\[
\begin{align*}
\text{EtO}_2\text{C} & + R^1\equiv & \xrightarrow{\text{EtO}_2\text{C}} \\
\text{H}_2\text{N} & \begin{array}{c}
\text{Me}\end{array} + R^2\equiv & \xrightarrow{\text{DMSO, MW}} \text{EtO}_2\text{C} \\
\text{O} & \begin{array}{c}
\text{R}^1\end{array} & \xrightarrow{\text{170 °C, 20 min}} \\
\text{Me} & \begin{array}{c}
\text{R}^2\end{array} & \text{EtO}_2\text{C}
\end{align*}
\]

\[\begin{array}{c}
\text{EtO}_2\text{C} \\
\text{Me} & \begin{array}{c}
\text{R}^1\end{array} & \begin{array}{c}
\text{R}^2\end{array} & \text{EtO}_2\text{C}
\end{array}\]

c) Oxidation Reactions: Sharpless, et al. have synthesized diols from olefins. \(^{16}\)

\[
\begin{align*}
\text{K}_2\text{OsO}_4\text{(OH)}_4, \text{NMO, citric acid} & \xrightarrow{i\text{BuOH} / \text{H}_2\text{O}} \text{MW, 120 °C, 150 min} \\
\text{NMO} = 4\text{-methylmorpholine N-oxide}
\end{align*}
\]

\[
\begin{array}{c}
\text{EtO}_2\text{C} \\
\text{Me} & \begin{array}{c}
\text{OH}\end{array} & \begin{array}{c}
\text{H}\end{array} & \begin{array}{c}
\text{H}\end{array} & \begin{array}{c}
\text{H}\end{array} & \begin{array}{c}
\text{H}\end{array} & \begin{array}{c}
\text{OH}\end{array} & \begin{array}{c}
\text{H}\end{array} & \begin{array}{c}
\text{H}\end{array}
\end{array}
\]
3.2.2 Present Work

This section describes the syntheses of 2-[(2,4-difluoro-6-iodophenyl)-carbonyl]-N-arylhydrazine carbothioamide in ethanol (Scheme 3.2.2)

Scheme 3.2.2

3.2.3 Results and Discussion

All the recorded melting points were determined in open capillary tubes and are uncorrected. Purity of the compounds was checked by TLC on silica gel G plates.

Table 3.2.1: Characterization data of 2-[(2,4-difluoro-6-iodophenyl)-carbonyl]-N-arylhydrazine carbothioamide
<table>
<thead>
<tr>
<th>Compd</th>
<th>Ar</th>
<th>M.P (°C)</th>
<th>Ultrasound</th>
<th>Microwave</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td>Time (min)</td>
<td>Yield (%)</td>
<td>Time (min)</td>
</tr>
<tr>
<td>16a</td>
<td>2-methyl phenyl</td>
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<tr>
<td>16b</td>
<td>3-methoxy phenyl</td>
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<td>88</td>
<td>3.0</td>
</tr>
<tr>
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<td>4-methoxy phenyl</td>
<td>158</td>
<td>31</td>
<td>86</td>
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<td>16d</td>
<td>4-methyl phenyl</td>
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<td>28</td>
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<td>2.5</td>
</tr>
<tr>
<td>16e</td>
<td>4-bromo phenyl</td>
<td>164</td>
<td>33</td>
<td>82</td>
<td>3.5</td>
</tr>
</tbody>
</table>

γ<sub>max</sub> (KBr disk / cm<sup>-1</sup>) (16e): 3320, 3203, 2922, 1699, 1511, 1203.
MS (ESI, 70eV): m/z = 513 (M+H)<sup>+</sup> (16e) with all isotopic and other peaks.

### 3.2.4 Experimental

**Method [A]: (conventional method):** Equimolar amount (0.01 mole) of acid hydrazide 15 and aryl isothiocyanates was dissolved in ethanol (12–15mL) and refluxed for 60 minutes. The reaction was monitored by TLC. On completion, the solid that precipitated was filtered and recrystallized from ethanol to give 16. This typical experimental procedure was followed to prepare other analogs of this series.
Compounds 16a-e were synthesized by the above general procedure and listed in Table 3.2.1 with their characterization data.

**Method [B]: (ultrasound method):** Equimolar amount (0.01 mole) of acid hydrazide 15 and aryl isothiocyanates was dissolved in ethanol (ca 15mL) and the reaction mixture was subjected for ultrasound irradiation for 30–35 minutes. Progress of reaction was monitored by TLC. The precipitated solid was filtered and recrystallized from ethanol to give 16. This typical experimental procedure was followed to prepare other analogs of this series.
Compounds 16a-e were synthesized by the above general procedure and listed in Table 3.2.1 with their characterization data.
Method [C]: (MW method): Equimolar amount (0.01 mole) of acid hydrazide 15 and aryl isothiocyanates when dissolved in ethanol (ca 25mL) was irradiated in a borosilicate glass beaker (50 mL) inside a MW oven for 3–4 minutes at an output of 300 watts power, with short interruption of 15 seconds to avoid excessive evaporation of solvent. Progress of reaction was monitored by TLC. The reaction mixture was cooled and poured over crushed ice containing water. Solid that separated was filtered and recrystallized with ethanol to give 16. This typical experimental procedure was followed to prepare other analogs of this series.

Compounds 16a-e were synthesized by the above general procedure and listed in Table 3.2.1 with their characterization data.

3.2.5 References
SECTION C:
Cyclization of thiosemicarbazide in presence of a dehydrating agent at room temperature to yield N-aryl-5-(2,3,4,6-tetrafluoro-phenoxy)-1,3,4-thiadiazole-2-amine

3.3.1 Introduction and Literature search
During recent years there has been intense investigation of different classes of thiadiazole compounds, many of which are known to possess biological properties. Among them 1,3,4-thiadiazoles have long been the subject of pharmaceutical interest due to its application in diverse fields and it is probably due to the strong aromaticity of the ring system, which leads to in vivo stability and generally lack of toxicity for higher vertebrates, including humans. When diverse functional groups that interact with biological receptors are attached to this ring, compounds possessing outstanding properties are obtained. 5-amino-1,3,4-thiadiazole derivatives such as the thio 28, a compound used as a radioprotective agent, as well as an antitumor and gastroprotective drug. Acetazolamide 29, a first non-mercurial diuretic drug used for antiglaucoma, antiepileptic, antiulcer drug. Another group have reported amino 1,3,4-thiadiazole 30, for the treatment of CA deficiency syndrome, a rare but dramatic genetic disease caused due to lack of enzyme CA II in human beings. Also its metal complexes (ie amino 1,3,4-thiadiazole 30) showed antifungal activity against Aspergillus and Candida spp.

![Chemical structures](image)

The treatment of mycobacterial infection, especially tuberculosis, has become an important problem due to the emergence of multidrug-resistance therefore Oruc, E.; et al. have synthesized 1,3,4-thiadiazole 31, with the aim of new antituberculosis drugs development. Recently nitroimidazole ring linked 1,3,4-thiadiazole 32, were
synthesized aimed at the development of new compounds which would act as anti-leishmanial agent\textsuperscript{12,13} (anti-parasitic properties) against promastigotes form of \textit{Leishmania major}.

\begin{equation}
\text{Ar} = \text{C}_6\text{H}_5, 4-\text{XC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4

\text{R}^1 = \text{H, X, Me, NO}_2
\end{equation}

Survey of Synthetic Procedures: The syntheses of 1,3,4–thiadiazole is discussed in terms of the number of bonds being formed and by ring transformation. Thiadiazole syntheses by one one–bond formation are exemplified by the cyclization of an acylated thiosemicarbazide. The most common two–bond formation takes place via 1,3–dipolar cycloadditions.

a) Formation of One Bond.

i) Cyclization: Monothiodiacylhydrazines, derieved from thiosemicarbazides cyclize in the presence of acid catalyst to give 1,3,4–thiadiazole.

\begin{equation}
\text{R}^1 \text{NH-NH} \rightarrow \text{R}^1 \text{N} = \text{N}\text{R}^2
\end{equation}

Phosphoryl chloride,\textsuperscript{14} acid chlorides,\textsuperscript{15} H$_2$SO$_4$,\textsuperscript{16,17} PPA,\textsuperscript{18} H$_3$PO$_4$,\textsuperscript{19} MeSO$_3$H,\textsuperscript{20} AcOH\textsuperscript{21} etc also induce cyclization. Use of MW irradiation\textsuperscript{22,23} results increase in yield and reduction of time.

Oxidative cyclization of thioacylhydrazone gives 1,3,4–thiadiazoles. Common oxidants include bromine,\textsuperscript{24} ferric chloride\textsuperscript{25} and potassium permanganate.\textsuperscript{26}
b) Formation of Two Bonds.

i) Diazenes and hydrazines with a sulfur source: Dehydration of DMF, with thionyl chloride gives formamidoyl chloride which reacts with N–N‘-diformylhydrazine to give diazene which cyclizes in presence H₂S to give 1,3,4-thiadiazole.

A variety of sulfur–releasing reagents can be used for example phosphorous pentasulfide,²⁷ carbon disulfide,²⁸ hydrogen sulfide²⁹ etc. The alternative use of Lawesson’s reagent³⁰ gives higher yield, shorter reaction time and cleaner reactions³¹ under MW conditions.³²
ii) Reaction of Thiohydrazide derivatives with a carbon source in presence of
dehydrating agents like POCl₃, H₂SO₄, PPA etc.

\[
\begin{align*}
\text{H₂N} & \text{NH} \quad + \quad \text{R¹ COOH} \\
\text{S} & \quad \text{NH-NH} \\
\rightarrow & \quad \text{R¹} \\
\end{align*}
\]

Acid esters and acid chlorides react with thiosemicarbazides to give 1,3,4-thiadiazole.

a) From Amidrazone: Amidrazone are cyclized to thiadiazoles in presence of CS₂.

\[
\begin{align*}
\text{Cl} & \quad \text{NH} \\
\text{N} & \quad \text{NH} \\
\rightarrow & \quad \text{CS₂, EtOH, reflux, 1h} \\
\end{align*}
\]
c) From other heterocycles: 1,3,4-Oxadiazoles\textsuperscript{39} react with thiourea to give thia diazoles.

\[
\begin{array}{c}
\text{R}_1^1 \text{O} \text{N} \text{N} \text{R}_2^2 + \text{H}_2 \text{N} \text{N} \text{NH}_2 & \xrightarrow{150 \degree C, 30h} & \text{R}_1^1 \text{S} \text{N} \text{N} \text{R}_2^2 + \text{H}_2 \text{N} \text{N} \text{NH}_2 \\
\end{array}
\]

Similarly 5-aminotetrazole\textsuperscript{40} reacts with 1,2,3-dithiazolium chloride to give thia diazole.

\[
\begin{array}{c}
\text{N} \text{N} \text{N} \text{NH}_2 + \text{Cl}_2 \text{Cl} \rightarrow \text{N} \text{N} \text{N} \text{Cl} \text{N} \text{Cl} \rightarrow \text{N} \text{N} \text{N} \text{NC} \text{Cl} \\
\end{array}
\]

Imidazole carboxaldehyde\textsuperscript{41,42} on treatment with thiosemicarbazide gives thia diazole.

\[
\begin{array}{c}
\text{O}_2 \text{N} \text{N} \text{N} \text{CH}_3 \text{CHO} \xrightarrow{\text{i}} \text{N} \text{N} \text{N} \text{Me} \xrightarrow{\text{ii}} \text{O}_2 \text{N} \text{N} \text{N} \text{NH}_2 \\
\end{array}
\]

\text{i: thiosemicarbazide, EtOH, HCl, reflux}
\text{ii: ammonium ferric sulfate, H}_2\text{O}, reflux

\textbf{3.3.2 Present Work}

This section explains cyclization of thiosemicarbazide in presence of a dehydrating agent at room temperature to yield N-aryl-5-(2,3,4,6-tetrafluoro-phenoxy)-1,3,4-thia diazole-2-amine.

(Scheme 3.3.1)
3.3.3 Results and Discussion

All the recorded melting points were determined in open capillary tubes and are uncorrected. $^1$H NMR spectra were recorded on Varian 300 MHz spectrophotometer in CDCl$_3$ as a solvent and TMS as an internal standard. Peak values are shown in δ ppm and $J$ values are in Hertz. Purity of the compounds was checked by TLC on silica gel G plates.

Table 3.3.1: Characterization data of N-aryl-5-(2,3,4,6-tetrafluoro-phenoxy)-1,3,4-thiadiazole-2-amine.

<table>
<thead>
<tr>
<th>Compd</th>
<th>Ar</th>
<th>M.P. (°C)</th>
<th>Ultrasound</th>
<th>Microwave</th>
<th>Conventional</th>
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<tr>
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<td>28</td>
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<td>3.5</td>
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<tr>
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<td>30</td>
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<td>phenyl</td>
<td>208</td>
<td>28</td>
<td>70</td>
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\( \gamma_{\text{max}} \) (KBr disk/ cm\(^{-1}\)) (17c): 3259, 1605, 1244,1034.

\( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) (17c): \( \delta \) 3.73 (s, 3H), 5.54 (s, 2H), 6.94 (d, 2H), 7.51 (d, 2H), 7.65 (s, 1H), 10.31 (s, 1H, exchangeable with D\(_2\)O).

MS (ESI, 70eV): m/z = 385 (M+H\(^+\)) (17c) with all isotopic and other peaks.

### 3.3.4 Experimental

**Method [A]: (conventional method):** Equimolar amount (0.01 mole) of thiosemicarbazide 14 and 15 mL of conc. H\(_2\)SO\(_4\) were stirred in a 100 mL RBF at 25–27 °C for 2 hours. Progress of reaction was monitored by TLC. The reaction mixture was then poured over crushed ice, to obtain solid which was filtered and recrystallized from water/DMF to give 17. This typical experimental procedure was followed to prepare other analogs of this series.

Compounds 17a-e were synthesized by the above general procedure and listed in

**Table 3.3.1** with their characterization data.

**Method [B]: (ultrasound method):** Equimolar amount (0.01 mole) of thiosemicarbazide 14 and

15 mL of conc. H\(_2\)SO\(_4\) were stirred in a 100 mL RBF and then subjected to ultrasound irradiation for 30 minutes. Progress of reaction was monitored by TLC. After completion of reaction mixture was poured over crushed ice. Solid obtained was separated by filtration and then recrystallized from water/DMF to give 17. This typical experimental procedure was followed to prepare other analogs of this series.

Compounds 17a-e were synthesized by the above general procedure and listed in

**Table 3.3.1** with their characterization data.

**Method [C]: (MW method):** Equimolar amount (0.01 mole) of thiosemicarbazide 14 and 15 mL of conc. H\(_2\)SO\(_4\) was irradiated in a borosilicate glass beaker (50 mL) inside a MW oven for 2–3 minutes at an output of 300 watts power, with short interruption of 15 seconds to avoid excessive evaporation of solvent. Progress of reaction was monitored by TLC. The reaction mixture was cooled and poured over crushed ice
containing water to give 17. This typical experimental procedure was followed to prepare other analogs of this series.
Compounds 17a-e were synthesized by the above general procedure and listed in Table 3.3.1 with their characterization data.

3.3.5 References
Analysis Name: 26059900.d  Instrument: LC-MSD-Trap SL  Print Date: 05/26/2009 01:22:44 PM
Method: ZPC.m  Operator: drama  Acq. Date: 05/26/2009 01:17:48 PM
Sample Name: ZPC/756/09 A  +VE MODE
Analysis Info: ZPC/756/09 A ST 1  +VE MODE

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<td>12.00 Volt</td>
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<tr>
<td>Oct 2 DC</td>
<td>3.00 Volt</td>
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</table>

Mass: N-(4-methoxyphenyl)-5-[3,7,5,4,6-tetrafluorophenoxyl]methyl]-1,3,4-thiadiazol-2-amine (17a):

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SECTION D:
Syntheses of thiadiazole using sulfuric acid, which results in cyclization of thiosemicarbazide to give 5-(2,4-difluoro-6-iodophenyl)-N-aryl-1,3,4-thiadiazole-2-amine

3.4.1 Introduction and Literature search
The development of 1,3,4-thiadiazole chemistry is linked to the discovery of phenylhydrazine by Fischer and of hydrazine by Curtius in the 19th century. Due to the electronegativity of the two nitrogen atoms in the rings, the carbon atoms have low electron density, and, consequently, 1,3,4-thiadiazole with functional groups are important intermediates, for example in halogeno-1,3,4-thiadiazoles, the halogen atom is readily displaced by nucleophiles. Bacchetti et al1,2 have studied the reaction between aromatic diazoketones and thiocarbonyl chloride. Chlorothiadiazoles react readily with nucleophiles to give a series of 5-substituted-2-acyl-thiadiazoles. (Scheme 3.4.1)

![Scheme 3.4.1](image)

Nucleophilic reaction at the carbon atoms of 1,3,4-thiadiazoles occur due to the electron deficient nature of this ring.3-6 (Scheme 3.4.2)
Electrophilic substitution reaction on the carbon atom of 1,3,4–thiadiazoles are rare due to the low electron density of the ring carbons. No examples of direct oxidation of 1,3,4–thiadiazoles sulfur to sulfoxide or sulfone have been reported. Electrophilic reactions like N–alkylation with acyl and cyanogen halides as well as Mannich salts have also been reported. (Scheme 3.4.3)

Now we shall focus on the reactivity of substituents attached to ring carbon atoms.

a) Carbon Substituents: Lithiation with LDA and quenching with aldehydes or ketones gave mono or bis–hydroxyl product depending on the equivalent of the base used. It can also be acylated with sodium hydride.
b) Nitrogen Substituents: Selective functionalization of the exocyclic nitrogen can be alkylated to secondary and tertiary amines,\textsuperscript{11} reaction with nitriles gives amidines,\textsuperscript{12} isocyanates afford ureas,\textsuperscript{13,14} acid chlorides give amide\textsuperscript{15,16} etc.

c) Oxygen Substituents: Dealkylation of alkoxy 1,3,4–thiadiazole is possible under acidic condition to give thiadiazolone.\textsuperscript{17}
d) Sulfur Substituents: Sulfur–substituent groups at the C–2 and/or C–5 undergo alkylation,\textsuperscript{18,19} and can also be converted to either sulfoxides or sulfones depending on the oxidation conditions.\textsuperscript{20,21}

3.4.2 Present Work

This section describes the syntheses of thiadiazole using sulfuric acid, which results in cyclization of thiosemicarbazide to give 5–(2,4–difluoro–6–iodophenyl)–N–aryl–1,3,4–thiadiazole–2–amine.

(Scheme 3.4.4)
3.4.3 Results and Discussion

All the recorded melting points were determined in open capillary tubes and are uncorrected. $^1$H NMR spectra were recorded on Varian 400 MHz spectrophotometer in DMSO–d$_6$ as a solvent and TMS as an internal standard. Peak values are shown in δ ppm and $J$ values are in Hertz. Purity of the compounds was checked by TLC on silica gel G plates.

**Table 3.4.1:** Characterization data of 5–(2,4–difuoro–6–iodophenyl)–N–aryl–1,3,4–thiadiazole–2–amine.
<table>
<thead>
<tr>
<th>Compd</th>
<th>Ar</th>
<th>M.P (°C)</th>
<th>Ultrasound</th>
<th>Microwave</th>
<th>Conventional</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time (min)</td>
<td>Yield (%)</td>
<td>Time (min)</td>
</tr>
<tr>
<td>18a</td>
<td>2-methyl phenyl</td>
<td>218</td>
<td>30</td>
<td>80</td>
<td>3.0</td>
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<td>18b</td>
<td>3-methoxy phenyl</td>
<td>223</td>
<td>30</td>
<td>87</td>
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<td>18c</td>
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<td>18e</td>
<td>4-bromophenyl</td>
<td>230</td>
<td>35</td>
<td>87</td>
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</tr>
</tbody>
</table>

$\gamma_{\text{max}}$ (KBr disk/ cm$^{-1}$) ($18\text{e}$): 3480, 1595, 1250.

$\delta_{\text{H}}$ (400 MHz, DMSO–d$_6$) ($18\text{e}$): $\delta$ 3.73 (s, 3H), 5.54 (s, 2H), 6.94 (d, 2H), 7.51 (d, 2H), 7.50 (d, 2H), 7.71 (d, 2H), 10.81 (s, 1H, exchangeable with D$_2$O).

MS (ESI, 70eV): m/z = 495 (M+H)$^+$ ($18\text{e}$) with all isotopic and other peaks.

3.4.4 Experimental

**Method [A]: (conventional method):** Equimolar amount (0.01 mole) of thiosemicarbazide 16 and 15 mL of conc. H$_2$SO$_4$ were stirred in a 100 mL RBF at 25–27 °C for 2 hours. Progress of reaction was monitored by TLC. The reaction mixture was then poured over ice, to obtain solid which was filtered and recrystallized from water/DMF to give 18. This typical experimental procedure was followed to prepare other analogs of this series.

Compounds $18\text{a-e}$ were synthesized by the above general procedure and listed in Table 3.4.1 with their characterization data.

**Method [B]: (ultrasound method):** Equimolar amount (0.01 mole) of thiosemicarbazide 16 and 15 mL of conc. H$_2$SO$_4$ were stirred in a 100 mL RBF and then subjected to ultrasound irradiation for 30 minutes. Progress of reaction was monitored by TLC. After completion of reaction mixture was poured over crushed ice. Solid obtained was separated by filtration and then recrystallized from water/DMF to
give 18. This typical experimental procedure was followed to prepare other analogs of this series. Compounds 18a-e were synthesized by the above general procedure and listed in Table 3.4.1 with their characterization data.

**Method [C]: (MW method):** Equimolar amount (0.01 mole) of thiosemicarbazide 16 and 15 mL of conc. H₂SO₄ was irradiated in a borosilicate glass beaker (50 mL) inside a MW oven for 2–3 minutes at an output of 300 watts power, with short interruption of 15 seconds to avoid excessive evaporation of solvent. Progress of reaction was monitored by TLC. The reaction mixture was cooled and poured over crushed ice. Solid that separated was filtered and recrystallized with water/DMF to give 18. This typical experimental procedure was followed to prepare other analogs of this series. Compounds 18a-e were synthesized by the above general procedure and listed in Table 3.4.1 with their characterization data.

### 3.4.5 References

FT-IR: N-(4'-diaminophenyl)-5,5',4'-difluoro-4,4'-biphenyl-1,3,4-thiadiazole-2-amine (1b):