Chapter - 3

Synthesis of 1,3-Bis-(N-substitutedthioamido) guanidine
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Abstract

The interaction of guanidine carbonate with (i) phenylisothiocyanate, (ii) ethylisothiocyanate, (iii) p-chlorophenylisothiocyanate, (iv) p-tolylisothiocyanate, (v) methylisothiocyanate and (vi) t-butylisothiocyanate in acetone-ethanol medium have been investigated to obtain 1,3-bis (N-phenylthioamido) guanidine, 1,3-bis (N-ethylthioamido) guanidine, 1,3-bis (N-p-chlorophenylthioamido) guanidine, 1,3-bis (N-p-tolylthioamido) guanidine, 1,3-bis (N-methylthioamido) guanidine and 1,3-bis (N-t-butylthioamido) guanidine, respectively. The compounds synthesized in these reactions were characterised on the basis of conventional elemental analysis, chemical characteristics and through IR and NMR spectral studies.

Introduction

Guanidine, guanidine salts possess pharmacological, biological, medicinal and industrial importance. The interaction of aryl/alkyl amines and different isothiocyanates have been briefly studied. The interactions of dicyandiamide and aryl/alkylisothiocyanate have been also investigated in this laboratory. The compounds isolated in these reactions possesses pharmaceutical, biological and medicinal values. Sulphaguanidine is best antibiotic in sulpha drugs. Thiocarbamidino derivatives possesses medicinal and pharmaceutical importance. Guanidine, guanidine salts and derivatives of guanidine have been invariably used, in this synthesis of 6-membered nitrogen containing compounds, particularly pyrimidine derivatives and certain other nitrogen and sulphur containing heterocyclic compounds. As a part of research work, the presently being undertaken in this laboratory in the synthesis of newer type of heteroacyclic and heterocyclic compounds. It appeared interesting to
investigate the reactions of guanidine carbonate with certain aryl/alkyl isothiocyanate in acetone-ethanol medium. (Scheme - 1)

**SCHEME - 1**

\[
\begin{align*}
\text{H}_2\text{N–C–NH}_2 + 2 \text{S} = \text{C} = \text{N} - \text{R} \rightarrow \text{R–NH–C–NH–C–NH–C–NH–R} \\
\text{Acetone-Ethanol} \\
\text{NH.H}_2\text{CO}_3 \\
\text{S} \quad \text{NH} \quad \text{S}
\end{align*}
\]

Where, \( \text{R} = \) phenyl, \( p \)-chlorophenyl, \( p \)-tolyl, ethyl, methyl, \( t \)-butyl

**Result and Discussion**

(i) **Synthesis of 1,3-bis (N-phenylthioamido) guanidine (5a):**

1,3-Bis (N-phenylthioamido) guanidine (5a) was prepared by refluxing the reaction mixture of guanidine carbonate (1) and phenylisothiocyanate (2a,) in 1:2 molar ratios in acetone-ethanol medium over steam bath for 14 hrs. The shining fine yellow crystals were separated on cooling the solution. It was filtered and washed with cold water several times. It was recrystallized with ethanol, yield 82%, m.p. 182-183\(^\circ\)C.

The probable reaction mechanism of the formation of (5a) may be stated as follows.

\[
\begin{align*}
\text{H}_2\text{N–C–NH}_2 + 2 \text{S} = \text{C} = \text{N–}\text{N} & \rightarrow \text{N–}\text{N} \\
\text{NH.H}_2\text{CO}_3 & \text{Acetone-ethanol} \\
\text{S} \quad \text{NH} \quad \text{S}
\end{align*}
\]
Properties of (5a):

1. It was shiny fine yellow crystalline solid having m.p. 182-183°C.
2. It gave positive test for nitrogen and sulphur.
3. It was found to be desulphurizable when warmed with alkaline lead acetate solution.
4. It was found to be soluble in hot ethanol, benzene, acetone and insoluble in water and ether.
5. The benzene solution of compound when treated with pure and dry carbon disulphide a yellow colour was developed. This indicates the presence of basic imino group (=NH) in the compound.
6. It formed picrate m.p. 177-178°C.
7. Elemental analysis:

<table>
<thead>
<tr>
<th>Elements</th>
<th>Found</th>
<th>Calculated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>53.59</td>
<td>54.71</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>3.88</td>
<td>4.56</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>21.05</td>
<td>21.27</td>
</tr>
<tr>
<td>Sulphur</td>
<td>19.27</td>
<td>19.45</td>
</tr>
</tbody>
</table>

8. From analytical data, the molecular formula was found to be C_{15}H_{15}N_{5}S_{2}.
9. **IR Spectrum**: The IR spectrum of compound (5a) was carried out in KBr pellets and is reproduced on Plate No. IR-3.1. The important absorption can be correlated as follows.
<table>
<thead>
<tr>
<th>Absorption observed (cm⁻¹)</th>
<th>Assignment</th>
<th>Absorption expected (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3387.3</td>
<td>NH stretching</td>
<td>3500-3100₁₃₋₁₆</td>
</tr>
<tr>
<td>3147.7</td>
<td>C–H (Ar) stretching</td>
<td>3150-3000₁₇</td>
</tr>
<tr>
<td>1666.3</td>
<td>C=NH stretching</td>
<td>1789-1471₁₈</td>
</tr>
<tr>
<td>1575.9</td>
<td>&gt; C=NH (imino) grouping</td>
<td>1789-1471₁₈</td>
</tr>
<tr>
<td>1395.3</td>
<td>C–N stretching</td>
<td>1340-1250₁⁹</td>
</tr>
<tr>
<td>1178.0</td>
<td>N &gt; C = S grouping</td>
<td>1200-1050²₀⁻²¹</td>
</tr>
<tr>
<td>746.9</td>
<td>C–S stretching</td>
<td>800-600²²</td>
</tr>
</tbody>
</table>

10. **PMR**: The PMR spectrum¹⁴,¹⁷,¹₈,¹⁹,²¹ of compound (5a) was carried out in DMSO-d₆ and CDCl₃ and reproduced on Plate No. PMR-3.1. This spectrum distinctly displayed signals due to Ar–NH protons at δ 7.99-8.0 ppm, Ar–H protons at δ 6.9 ppm, NH protons at δ 3.25-3.27 ppm. The signals at δ 2.55 is due to moisture in DMSO-d₆ and 1.24 is due to DMSO.

From the above properties and spectral analysis the compound (5a) was assigned the structure as 1,3-Bis (N-phenylthioamido) guanidine.

![Structure of 5a](image)

(5a)

Similarly, 1,3-bis (N-ethylthioamido) guanidine (5b), 1,3-bis (N-p-chlorophenylthioamido) guanidine (5c), 1,3-bis (N-p-tolylthioamido) guanidine (5d), 1,3-bis (N-methylthioamido) guanidine (5e) and 1,3-bis (N-t-
butylthioamido) guanidine (5f) were prepared by the interaction of (1) with ethylisothiocyanate, p-Cl-phenylisothiocyanate, p-tolylisothiocyanate, methyl isothiocyanate and t-butylisothiocyanate, respectively, by the above mention method in Experiment No. 2 to Experiment No. 6 and listed in Table-1.

Table - 1*

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Expt. No.</th>
<th>1,3-Bis (N-substitutedthioamido) guanidine</th>
<th>Yield (%)</th>
<th>m.p. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>02</td>
<td>(N-ethylthioamido)</td>
<td>68</td>
<td>172</td>
</tr>
<tr>
<td>2</td>
<td>03</td>
<td>(N-p-chlorophenylthioamido)</td>
<td>82</td>
<td>194</td>
</tr>
<tr>
<td>3</td>
<td>04</td>
<td>(N-p-tolythioamido)</td>
<td>72</td>
<td>189</td>
</tr>
<tr>
<td>4</td>
<td>05</td>
<td>(N-methylthioamido)</td>
<td>82</td>
<td>160</td>
</tr>
<tr>
<td>5</td>
<td>06</td>
<td>(N-t-butylthioamido)</td>
<td>62</td>
<td>169</td>
</tr>
</tbody>
</table>

*Gave satisfactory C, H, N, and S elemental analysis.

Experimental

The melting points of all the synthesised compounds were recorded using hot paraffin bath and are uncorrected. The carbon and hydrogen analysis was carried out on Carlo-Ebra-1106 analyser, nitrogen estimation was carried out on Colman-N-analyser-29. IR spectra were recorded on Perkin Elmer spectrometer in the range 4000-400 cm^{-1} in Nujol mul as KBr pellets. PMR spectra were recorded on Bruker AC-300F spectrometer with TMS as internal standard using CDCl_{3} and DMSO-d_{6} as solvent. The purity of the compound was checked on Silica Gel-G plates by TLC with layer thickness of 0.3 mm. All chemicals used were of AR grade (India Make) guanidine carbonate (Lanshter Make, Germany).
1) **Aryl/Alkylisothiocyanate (2a):**

Aryl/Alkylisothiocyanate were prepared by the procedure described in "Vogel's Text Book of Practical Organic Chemistry". t-butyliisothiocyanate was prepared by the procedure given by Schmidte et. al.

**Experiment No. 1:**

**Synthesis of 1,3-Bis (N-phenylthioamido) guanidine (5a):**

A mixture of guanidine carbonate (1) (0.01 M), and phenylisothiocyanate (2a) (0.02 M) was refluxed over steam bath for 14 hrs. in presence of acetone-ethanol (50 ml) medium. During boiling the suspended guanidine carbonate went into solution. The mixture was cooled and solvent was distilled off. Fine yellow crystals were separated out. It was washed with cold water several times. It was recrystallized from ethanol and identified as 1,3-Bis (N-phenylthioamido) guanidine (5a), yield 78%, m.p. 182-183°C.

**Experiment No. 2:**

**Synthesis of 1,3-Bis (N-ethylthioamido) guanidine (5b):**

A mixture of guanidine carbonate (1) (0.01 M) and ethylisothiocyanate (2) (0.02 M) was refluxed over steam bath for 14 hrs. in presence of acetone-ethanol (50 ml) medium. During boiling the suspended guanidine carbonate went into solution. The mixture was cooled and solvent was distilled off. Ivory crystals were separated out. It was washed with cold water several times. It was recrystallized from ethanol and identified as 1,3-Bis (N-ethylthioamido) guanidine (5b), yield 68%, m.p. 172°C.
Experiment No. 3:

Synthesis of 1,3-Bis (N-p-chlorophenylthioamido) guanidine (5c):

A mixture of guanidine carbonate (1) (0.01 M) and p-chlorophenylisothiocyanate (2a) (0.02 M) was refluxed over steam bath for 14 hrs. in presence of acetone-ethanol (50 ml) medium. During boiling the suspended guanidine carbonate went into solution. The mixture was cooled and solvent was distilled off. Pale yellow crystals were separated out. It was washed with cold water several times. It was recrystallized from ethanol and identified as 1,3-Bis (N-p-chlorophenylthioamido) guanidine (5c), yield 82%, m.p. 194°C.

Experiment No. 4:

Synthesis of 1,3-Bis (N-p-tolylthioamido) guanidine (5d):

A mixture of guanidine carbonate (1) (0.01 M) and p-tolylisothiocyanate (2a) (0.02 M) was refluxed over steam bath for 14 hrs. in presence of acetone-ethanol (50 ml) medium. During boiling the suspended guanidine carbonate went into solution. The mixture was cooled and solvent was distilled off. Pale brown crystals were separated out. It was washed with cold water several times. It was recrystallized from ethanol and identified as 1,3-Bis (N-p-tolylthioamido) guanidine (5d), yield 72%, m.p. 189°C.

Experiment No. 5:

Synthesis of 1,3-Bis (N-methylthioamido) guanidine (5e):

A mixture of guanidine carbonate (1) (0.01 M) and methylisothiocyanate (2a) (0.02 M) was refluxed over steam bath for 14 hrs in presence of acetone-ethanol (50 ml) medium. During boiling the suspended guanidine carbonate went into solution. The mixture was cooled and solvent was distilled.
off. Lemon yellow crystals were separated out. It was washed with cold water several times. It was recrystallized from ethanol and identified as 1,3-Bis (N-methylthioamido) guanidine (5e), yield 82%, m.p. 160°C.

Experiment No. 6:

Synthesis of 1,3-Bis (N-t-butylthioamido) guanidine (5f):

A mixture of guanidine carbonate (1) (0.01 M) and t-butyl isothiocyanate (2a) (0.02 M) was refluxed over steam bath for 14 hrs. in presence of acetone-ethanol (50 ml) medium. During boiling the suspended guanidine carbonate went into solution. The mixture was cooled and solvent was distilled off. Pale yellow crystals were separated out. It was washed with cold water several times. It was recrystallized from ethanol and identified as 1,3-Bis (N-t-butylthioamido) guanidine (5f), yield 62%, m.p. 169°C.
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