PART-B

CHAPTER-1

INTRODUCTION
1.1. INTRODUCTION

Chapters 1-3 of part A deals with the research works which focused on the developing greener protocol for amide synthesis wherein the solvent-free conditions employed eradicated the limitations associated with the prevailing solution-phase protocols. In sequel, we envisaged the applicability of the solvent-free protocol towards the synthesis of heterocycles, the prevailing synthetic routes of which involve amide bond formation via the coupling of carboxylic acid/derivatives and amines as one of the steps. In this regard, perusal of literature suggests that synthetic strategies for thiazolidones (N and S containing five membered heterocycles possessing a cyclic amide skeleton) involved the above said coupling. Thus, the present part deals with the synthesis of thiazolidone analogues, the details of which are presented in the forthcoming chapters 2-4.

Hence, it is pertinent to provide a brief background on the prevailing methodologies for thiazolidone synthesis.

1.2. Selective literature reports on synthesis of 2-iminothiazolidin-4-ones

1. From α-halo carboxylic acid derivatives
   - 2-Alkyl/arylimino-5-carbethoxythiazolidin-4-ones have been synthesized\(^1\) by the reaction of thiocarbamides with diethyl bromomalonate.
     \[
     \text{BrCOOH} + \text{R}_{2} \text{NH} \rightarrow \text{R}_{2} \text{CONH-S} \rightarrow \text{BrCOOEt} + \text{NH}_{2}\text{OH/H}_{2}\text{O}
     \]
   - Long-chain-substituted 2-imino-4-thiazolidinones were prepared\(^2\) in good yield by condensation of α-bromo-carboxylic acids with thiourea.
   - 5,5-Disubstituted-2-imino-4-thiazolidones were prepared\(^3\) by refluxing α-bromoacid chlorides with thiourea in glacial acetic acid.
- Oxiranyl- and thiiranyl-substituted 2-imino-thiazolidine-4-ones were prepared\textsuperscript{4} by refluxing thiourea with ethyl-2-chloro-3-(oxiran-2-yl)propanoate (X = O) or ethyl 2-chloro3-(thiiran-2-yl)propanoate (X = S).

\[ \text{H}_2\text{N}-\text{NH}_2 + \text{EtO}_2\text{O}+\text{Cl} \rightarrow \text{HN}-\text{S} \]

- 1-Carbaniloyl-2-oxo-3-pyrrolidinocarboxylates were brominated to give the intermediate α-halo keto ester. These underwent substitution and cyclization reactions with thiourea to afford\textsuperscript{5} spiro[pyrrolidinethiazolidine] in 29–40% yields.

\[ \text{O}_3\text{COOEt} \rightarrow \text{O}_3\text{Br} \rightarrow \text{O}_3\text{COOEt} + \text{H}_2\text{N}-\text{NH}_2 \rightarrow \text{O}_3\text{S} \]

- Reaction of ethyl-4-bromo-5-oxo-3-phenyl-4, 5-dihydroisoxazole-4-carboxylate with thiourea afford\textsuperscript{6} 2-amino-9-phenyl-7-oxa-1-thia-3,8-diaza[4.4]nona-2,8-diene-4,6-dione.

- Methyl-3-(7-(benzyloxy) quinolin-3-yl)-2-bromopropionate was cyclocondensed with thiourea in the presence of AcONa in ethanol under reflux condition to afford\textsuperscript{7} the 2-imino-5[(7-benzyloxy-3-quinolyl) methyl] thiazolidin-4-one which has an antihyperglycemic effect.

- 2-amino-5-(2-phenylbenzo[d]oxazol-5-l)methylthiazol-4(5H)-one has been prepared by Iijima et al.\textsuperscript{8} upon treatment with methyl acrylate and 2-phenylbenzo[d]oxazole followed by reaction with thiourea.
Sedlak et al.⁹ have reported the tandem intramolecular recyclization of 3-bromo-1-phenylpyrrolidin-2-ones with substituted thioureas in weakly basic media to afford the 2-imino thiazolidin-4-ones.

2. From chloroacetamides

Masaki et al.¹⁰ have prepared 2-aminothiazol-4(5H)-one by reaction of thiourea and 4-(2-chloroacetyl)piperazine-1-carbaldehyde.

2-imino-4-thiazolidinones¹¹ were prepared by the reaction of thiourea derivatives with N-(2-chloroacetyl)tetrahydroisoquinoline.

3. From cyanamide

Cyclocondensation of methyl 2-mercaptoacetate with cyanamide in methanol containing triethylamine afforded 2-amino-4-thiazolidinone.¹²

Heating thiolactic acid with cyanamide in water/ammonium hydroxide gave NH₃ gas and a precipitate of 2-imino-4-oxo-5-methylthiazolidine.¹³
4. From \( \alpha, \beta \) -unsaturated carboxylic acids

- Single-stage synthesis of 5-arylmethyl-2-iminothiazolidin-4-ones\(^{14}\) was achieved by reaction between \( \beta \)-arylacrylic acids and thiourea.

\[
\begin{align*}
R' & \equiv \text{H, Me, Ph, 4-MeC}_2\text{H}_5, 4-\text{ClC}_6\text{H}_4 \\
X & \equiv \text{Br, Cl, HSO}_4 
\end{align*}
\]

- Diethyl acetylene dicarboxylic ester has been treated with thiourea to afford (\( E \))-ethyl-2-(2-amino-4-oxothiazol-5(4\( H \))-ylidene)acetate\(^{15}\).

\[
\begin{align*}
\text{EtOOC} & \equiv \text{COOEt} \\
\text{thiourea} & \text{MeOH} 
\end{align*}
\]

- \( N \)-(maleoylamino)benzoic acids were treated with thiourea derivatives to give thiazolidones.\(^{16}\)

\[
\begin{align*}
\text{HOOC} & \equiv \text{N} \\
\text{thiourea} & \text{AcONa/AgO dioxane} 
\end{align*}
\]

5. From anhydrides or imides

- Reaction of 2-bromosuccinic anhydride and thiourea gave (\( E \))-2-(2-amino-4-oxothiazol-5(4\( H \))-ylidene)acetic acid.\(^{17}\)

\[
\begin{align*}
\text{Br} & \equiv \text{R} \\
\text{thiourea} & \text{R} = \text{Br, H} 
\end{align*}
\]

- Maleic anhydrides reacted with thiourea to give 1, 3-thiazolidone.\(^{18}\)

\[
\begin{align*}
\text{O} & \equiv \text{R} \\
\text{thiourea} & \text{R} = \text{H, Me, Ph} 
\end{align*}
\]

- 1-o-Tolyl-1\( H \)-pyrrole-2, 5-dione reacted with thiourea to give 2-(2-amino-4-oxo-4, 5dihydrothiazol-5-yl)-\( N \)-o-tolylacetamide\(^{19}\) in good yield.

\[
\begin{align*}
\text{Ph} & \equiv \text{N} \\
\text{thiourea} & \text{AcOH} 
\end{align*}
\]

- \( N \)-substituted maleimides were condensed with thiourea derivatives to afford 4-thiazolidone derivatives\(^{20}\) in 46-71% yields.
6. From epoxides
- The nucleophilic ring opening of gem-dicyano epoxides by \(N\)-substituted or \(N, N\) disubstituted thioureas lead to 2-imino-4-thiazolidinones,\(^{21}\) via a cyanocarbonyl intermediates.

- The reaction of (Z)-methylepoxysuccinic acid with thiourea gave 2-amino-thiazolidin-4-one.\(^{22}\)

- Ethylene oxide and thiourea in MeOH, gave 2-amino-4-keto-5-isopropylidene-2-thiazoline\(^{23}\) in very good yield.

7. From azoalkenes
- Thiourea easily reacted under very mild conditions with some conjugated azoalkenes in a one-pot reaction to give 39–88% of substituted thiazolinones.\(^{24}\)

8. From 2-(alkylthio)-2-thiazolin-4-ones
- Reactions of (E)-5-(arylmethylene)-2-(alkylthio)-2-thiazolin-4-ones with ammonium carbonate, aromatic primary amine and secondary amines afforded corresponding amino thiazolin-4-ones.\(^{25}\)
9. Miscellaneous methods

- Reaction of ethyl thiocyanatoacetate with aromatic aldehydes in presence of thiourea afforded (E)-5-arylidene-2-imino-4-thiazolidinones.26

\[
NC-S\overset{1.\text{thiourea}}{\longrightarrow}\overset{2.\text{ArCHO, EtOH}}{\longrightarrow} H_2N-S\overset{\text{Ar}}{\longrightarrow}
\]

- The reaction of 3-(trichloromethyl)pent-1-en-3-ol and aqueous thiourea afforded the corresponding 2-imino-4-thiazolidinones.27b

\[
\overset{\text{thiourea, EtOH}}{\longrightarrow}
\]

- The synthesis of substituted 5-(2-hydroxyethyl)-2-phenylimino-1,3-thiazolidin-4-ones28 were described, starting from phenylthioureas and 3-bromotetrahydrofuran-2-one under mild conditions.

\[
\overset{\text{Br}}{\longrightarrow} + H_2N-S\overset{\text{H}}{\longrightarrow} \overset{\text{R}}{\longrightarrow}
\]

Though discussions vide supra seem to be interesting with regard to the synthesis of thiazolidone skeletons, it is noted that most of them are solution-phase protocols using hazardous organic solvents.

Nowadays, much attention has been focused on the development of simple and eco-friendly synthetic procedures which constitute an important goal in organic synthesis. Many organic solvents that are used in large quantities in organic reactions are potential threat to human health and environment. Thus, redesign of chemical reactions under solvent-free condition and/or aqueous medium has gained immense popularity because of
its ease of set-up, mild conditions, and increased yield of product, cost efficiency and environmental-friendliness.

In connection with the above issues, in the present part, we have successfully achieved a solvent-free synthesis of thiazolidone analogues viz. I, II and III, the details of which are presented in the following chapters 2, 3 and 4 respectively.

1.3. REFERENCES