CHAPTER – 3

Synthesis and reactions of [(1-aza-2-benzimidazol-2-ylprop-1-enyl)amino]aminomethane-1-thiones

3.1 Introduction:

Thiosemicarbazone derivatives are biologically active molecules\(^1\), possessing activities such as anticancer\(^2\), antitumor\(^3\), antifungal\(^4\), antibacterial\(^5\) and anti-HIV\(^6\) to name just a few. In recent years, aryl and heteroaryl thiosemicarbazones have emerged as anticonvulsants\(^7\). Furthermore, derivatives of thiosemicarbazones such as thia
diazines, thiazolidinones and thiazoles exhibits various biological activities such as antituberculostatic\(^8\), local anesthetic\(^9\) etc. Thiazolidinone derivatives are known for their antimycobacterial properties\(^10\)-\(^12\). In view of these considerations, it was thought worthwhile to prepare thiosemicarbazone derivatives of 2-acetylbenzimidazole and study their modifications.

3.2 Literature Background:

Fernand et al. reported\(^13\) the condensation of ketones \(53\) with thiosemicarbazide \(54\) in the presence of an acid resulting in thiosemicarbazone \(55\). \(55\) on reaction with acetic anhydride in the presence of pyridine at 110 °C for 3 hrs yielded \(56\).
The transformation of 55 to 56 seems to occur by the mechanism shown below:

Singh et al. studied the synthesis of 58 by condensing 57 with thiosemicarbazide (54) in ethanol at 25 °C for 3 hrs giving 58.

Omar et al. reported the cyclization of thiosemicarbazones (59) with 60 giving 61.
Kabashima et al reported the cyclocondensation of thiosemicarbazones (62) with (63) yielding hydrazinothiazolidinones (64) and alkylidene aminothiazolidinones (65) depending on the R group.

Scheme – 3.4

Omar et al reported the synthesis of thiazolines (67) and thiazolidinones (68) by treating 66 with phenacyl bromides and with ethyl bromoacetate / sodium acetate under Hantzsch conditions.

Scheme -3.5
Jouad et al. studied the synthesis of diacetyl-substituted thiadiazolines (71) by treating 69 with acetic anhydride in dichloromethane solution giving 70 followed by heating of 70 in an oil bath for 25-27 hrs yielded 71.

Scheme -3.6

Badr studied the synthesis of novel 2, 5-disubstituted thiophene derivatives by condensing 72 with thiosemicarbazide resulting in 73. The latter, on reaction with phenacyl bromide in the presence of sodium acetate in ethanol under refluxing for 4-6 hrs, gave 74 and 75 on reaction 73 with acetic anhydride under refluxing for 3-5 hrs.

Scheme -3.7
Bhausaheb et al. reported\textsuperscript{20} the synthesis of 78 by treating 76 with thiosemicarbazide in the presence of sodium acetate in ethanol under reflux for 1 hr giving 77 followed by the reaction of the latter with acetic anhydride under reflux for 6–7 hrs giving 77.

\[ \text{SCHEME -3.8} \]

Holla et al reported\textsuperscript{21} the condensation of 79 with 80 by refluxing in ethanol for 3 hrs yielded 81.

\[ \text{SCHEME -3.9} \]

**3.3 Present work:**

From the literature data given above, it is evident that derivatives of thiadiazines, thiazolidinones and thiadiazol containing heterocyclic compounds have potential biological activity. Keeping this in view it was considered worthwhile to study the synthesis of
benzimidazole-2-yl thiosemicarbazone derivatives and their further chemical modifications.

2-Acetylbenzimidazole \((4)\) on treating with thiosemicarbazide in aq. methanol containing of glacial acetic acid under reflux for 4hrs yielded the previously reported \(^{22}82\).

![Scheme 3.10](image)

![Scheme 3.11](image)

\(82\) on reaction with \(p\)-chlorophenacyl bromide \((83)\) in ethanol under reflux for 2 hrs yielded the novel \(84\). The structure of the product was assigned on the basis of spectral and analytical data. Thus, its Infrared spectroscopy showed absorption 3340 (NH), 1581(C=N). Its Proton-NMR showed signals at 2.23 (s, 3H\(_3\)), 6.45 (s, 1H\(_3\)), 6.53 – 7.95 (m, 8H), 10.85 (s, 1H), 11.62 (s, 1H, -NH) and Its Cl mass spectrum showed ion peak at 368 (M\(^+\)1) corresponding to the mass of 367.
84 on reaction with m-CPBA in chloroform at (-) 10 °C for 6 hrs gave 85. The structure of the product was assigned on the basis of spectral and analytical data.

\[
\text{(84)} \xrightarrow{\text{m-CPBA / CHCl}_3 / (-)10^\circ \text{C} / 5 - 6 \text{ hrs}} \text{(85)}
\]

Scheme -3.12

82 on refluxing with chloroacetic acid in the presence of ammonium acetate in glacial acetic acid at 110 °C for 8 hrs in an oil bath gave 86. The structure of the product was assigned on the basis of spectral data. Thus, its Infrared spectroscopy showed peaks 3059 (NH), 1732 (-CO-). Its Proton-NMR showed signals at 1.93 (s, 3H,), 3.89 (t, 2H), 7.26 – 7.89 (m, 4H), 10.89 (s, 1H), 12.75 (s, 1H) and Its CI mass spectrum showed molecular peak at 274 (M^+1) corresponding to the mass of 273.

\[
\text{(82)} \xrightarrow{\text{CICH}_2\text{COOH / CH}_3\text{COONH}_4 / CH}_3\text{COOH / reflux / 8 hrs}} \text{(86)}
\]

Scheme -3.13

86 on condensation with benzaldehyde (87) in the presence of 5% alcoholic sodium hydroxide at room temperature for 5 hrs gave 88. The structure of the product was assigned on the basis of spectral data. Thus, its Infrared spectroscopy showed peaks at 3059 (-NH), 1732 (keto carbonyl), 1581 (C=N). Its Proton-NMR showed signals at
2.89 (s, 3H), 6.89 – 8.49 (m, 10H), 12.50 (s, 1H), 13.45 (s, 1H, -NH) and its CI mass spectrum showed ion peak at 362 (M$^+$+1) corresponding to the mass of 361.

82 on treating with 89 in ethanol in the presence of catalytic amount of acetic acid under reflux for 4-5 hrs gave 90. The structure of the product was assigned on the basis of spectral data. Thus, its Infrared spectroscopy showed absorption at 3059 (-NH), 1732 (carbonyl), 1581 (C=N). Its Proton-NMR showed signals at 2.65 (s, 3H), 6.90(s, 1H), 7.40 – 8.45 (m, 4H), 11.62 (s, 1H), 13.45 (s, 1H) and its CI mass spectrum showed peak at 333 (M$^+$+1) corresponding to the mass of 332.

82 on heating with acetic anhydride for 3 hrs gave 91. Thus, its Infrared spectroscopy showed absorption 3059 (-NH), 1732 (keto), 1581 (C=N). Its Proton-NMR showed signals at 2.45 (s, 3H), 3.52 (s, 3H), 7.23 – 8.34 (m, 4H), 11.52 (s, 1H), 13.24 (s, 1H) and its CI
mass spectrum showed ion peak at 318 (M+1) corresponding to the mass of 317.

Scheme - 3.16

Mechanism

91 on treating with 3 in ethanol under reflux for 3-4 hrs gave 92. The structure of the product was assigned on the basis of spectral. Thus, its Infrared spectroscopy showed absorption 3059 (stretching vibration), 1732 (keto carbonyl). Its Proton-NMR showed signals at 2.30 (s, 3H), 2.72 (s, 6H), 4.86 (s, 2H), 7.23 – 8.34 (m, 9H), and Its CI mass spectrum showed peak at 437 (M+1) corresponding to the mass of 436.
91 on refluxing with hydrazine hydrate at room temperature for 4hrs gave 93. The structure of the product was assigned on the basis of spectral. Thus, its Infrared spectroscopy showed peaks at 3059 (stretching vibration), 1732 (keto carbonyl), 3340 (NH₂). Its Proton-NMR showed signals at 2.62 (s, 3H,), 2.86 (s, 3H,), 3.86 (s, 2H,), 7.23 – 8.25 (m, 4H, four aryl protons), 12.32 (s, 1H,), and Its Cl mass spectrum showed ion peak at 276 (M⁺+1) corresponding to the mass of 275.
All the schemes are very briefly summarized in the Schemes -3.19, 3.20, 3.21.

Scheme -3.19

Scheme -3.20
Scheme 3.21

\[
\text{Reflux / 3hrs} \quad \text{AC}_2\text{O}
\]

\[
\text{Ph-C-CH}_2\text{Br}
\]

\[
\text{N}_2\text{H}_4\text{H}_2\text{O (aq) / RT / 3hrs}
\]

\[
\text{Ethanol / RT / 3hrs}
\]
Experimental Section:

1. **Preparation of 82 from 4**: A mixture of 2-acetylbenzimidazole (4) (1.60gms, 10mM) and thiosemicarbazide (0.79gms, 10mM) in aqueous methanol containing glacial acetic acid was refluxed for 3-4hrs. The solution was cooled to room temperature and poured into ice-cold water. The separated solid was filtered and dried.

2. **Preparation of 84 from 82**: A mixture of 82 (2.33gms, 10mM) and p-chlorophenacylbromide (2.31gms, 10mM) in ethanol refluxed for 3hrs. The solution was cooled to room temperature and poured the solution into ice-cold. The separated solid was filtered and dried.

3. **Preparation of 85 from 84**: To a stirred solution of 84 (1.66 gms, 5 mM) in chloroform (20 ml) at -10°C, meta chloro perbenzoic acid (0.87gms, 5 mM) was added and the mixture was stirred at room temperature for 3 hrs. At the end of this period, the excess chloroform was evaporated and the residue was poured into ice-cold water and neutralized with sodium bicarbonate. The separated solid was filtered and dried.

4. **Preparation of 86 from 82**: A mixture of ammonium acetate (0.38 gms, 5mM), 82 (1.16 gms, 5mM), and chloroacetic acid in acetic acid (20 ml) was refluxed at 110 °C for 8hrs. At the end of this period, the mixture was cooled to room temperature and poured into ice-cold water. The separated solid was filtered and dried.

5. **Preparation of 90 from 82**: To a compound of 82 (1.16 gms, 5mM) in ethanol and catalytic amount of glacial acetic acid, 89 (0.58 gms, 5mM) was added and refluxed on a water bath for 3hrs. At the
completion of the reaction the mixture was poured into ice-cold water.
The separated solid was filtered and dried.

6. **Preparation of 91 from 82**: A mixture of acetic anhydride (5ml) and 82 (1.16 gms, 5mM) was refluxed on an oil-bath for about 3 hrs. After the completion of the reaction the mixture was cooled to room temperature and poured into ice-cold water. The separated solid was filtered and dried.

7. **Preparation of 92 from 91**: To a solution of 91 (1.58gms, 5mM) in ethanol 83 (1.15 gns, 5mM) was added and stirred at room temperature for 3 hrs. The reaction mixture was poured into ice-cold water. The separated solid was filtered and dried.

8. **Preparation of 93 from 91**: To a solution of 91 (1.58gms, 5mM) in absolute ethanol hydrazine hydrate (0.25ml) was added and stirred at room temperature for 3 hrs. The reaction mixture was poured into ice-cold water. The separated solid was filtered and dried.