Synthesis of some Heterocyclic Compounds Derived from(5,6 diphenyl-1,2,4-triazine-3-thiol)

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Thiazolidinone,  
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ABSTRACT

The present work describe the synthesis of new heterocyclic compounds starting from reaction 5,6 diphenyl-1,2,4-triazine 3-thiol with ethyl chloro acetate afforded compound (1),then treatment with thiourea or urea afforded compound (2,3). p-Bromo phenacetyl bromide react with compounds (2,3) afforded compounds (4,5),treatment compound (1) with hydrazine hydrate to afforded 2-(5,6 di phenyl 1,2,4-triazin-3-yl)aceto hydrazide compound (6) . Azomethines (7,8) are were prepared through reaction of compound (6) with aromatic aldehyde, then (7,8) converted to thiaizolidinone derivatives (9,10) after treatment with 2-mercapto acetic acid Reaction of compound (6) with phenyl thiocyanate to give compound(11) and the product (11)react with ethyl chloro acetate afforded compound (12) , then reaction (5,6 di phenyl1,2,4-triazin-3-thiol with chloro acetic acid gave compound (13)followed by refluxing (13) with ortho phenylenediamine gave compound (14). All compounds were confirmed by their melting point, FT-IR spectrum, 1H-NMR spectrum for some of them.

INTRODUCTION

1,2,4-trazines and their condensed derivatives occupy a pivotal position in modern medicinal chemistry because of their high potential biological activities [1],the triazine structure is heterocyclic ring analogous to the six–membered benzene ring about with three carbons replaced by nitrogen . The three isomer of triazine are distinguished from each other by the position of their nitrogen atoms and are referred 1,2,3-triazine, 1,2,4-triazine , 1,3,5- triazine [2].1,2,4-triazine derivatives have been reported to posses aboard spectrum of bio activities including Anti-inflammatory[3],analgesic antihypertensive[4],cardiotoxic[5], neuroleptic nootropic [6], antihistaminergic[7], tuberculostatic[8], antiviral[9]. Thiazoles are important class of natural and synthetic compounds. Thiaizole derivatives display a wide range of biological activities such as.cardiotoxic,fungicidal sedative ,anaesthetic, bacterialid and anti-inflammatory[10]. The synthesis of thiazole derivatives is important for their wide range of pharmaceutical and biological properties[11]. Oxazoles are a common structural motif found in numerous molecules that displayantiviral ,antifungal, antibacterial, and antiproliferative activities[12]. Benzimidazoles are an important class of heterocycles that are frequently used in drug and agrochemical discovery programs[13] Benzimidazole derivatives have a broad antifungal spectrum and display their antifungal activities by blocking the polymerization of and tubulin subunits1.2. Antitubulin agents, especially benzimidazoles, disrupt microtubule function in eucaryotic organisms such as fungi, protozoa and helminthes[14].

EXPERIMENTAL

The melting points were determined in open capillary tubes on a Gallen Kamp melting point apparatus and were uncorrected .The FT-IR Spectra of some prepared derivatives were taken on Shimadzu-2N,FTIR-8400 S.1H-NMR Spectra of some prepared derivatives were recorded on a Varian-Mercury 300MHZ Spectrometer, d6-DSMO use as a solvent in 1H-NMR Spectra.

Preparation ethyl 2-(5,6 diphenyl-1,2,4-triazine-3yl thio)acetate (1)
Ethyl chloro acetate (1.1g,0.01 mol) was added dropwise to a stirred solution of 5,6 diphenyl-1,2,4-triazine-3thiol (2.6gm,0.01 mol) and KOH (0.56g,0.01 mol) in 20 mL absolute ethanol. The reaction mixture was refluxed for 7 hrs., after that cooled filtered the product and recrystallized from chloroform. Table (1)

Preparation N-carbamothioyl-2- (5,6 diphenyl-1,2,4-triazine-3yl thio) acetamide(2), N-carbamoyl-2-(5,6 di phenyl-1,2,4-triazine-3yl thio) acetamide(3).

A mixture of ethyl 2-(5,6 di phenyl)1,2,4-triazine-3yl thio)acetate (1) (1.7 gm,0.005 mole) with (0.005mole) thiourea or urea respectively in 25mL absolute ethanol were refluxed for 5hrs. After cooling ,the product was filtered the product, and recrystallized from ethanol. Table (1)

Preparation N-4(4-bromophenyl)thiazle-2-yl-2-(5,6diphenyl-1,2,4-triazine-3ylthio)acetamide(4) and N-4(4-bromophenyl)oxazol-2-yl-2-(5,6diphenyl-1,2,4-triazine-3ylthio)acetamide(5).

A mixture of compounds(2 or 3)(0.002mole) and (0.002mole) of bromo phenacyl bromide were dissolved in 20ml absolute ethanol .then refluxed for 4hrs.The mixture was cooled and neutralized with ammonium hydroxide solution ,the precipitated was filtered off and washed with water, recrystallized from ethyl acetate . Table (1)

Preparation 2-(5,6di phenyl)1,2,4-triazine-3yl thio)aceto hydrazide(6).

Ethyl 2-(5,6 di phenyl)1,2,4-triazine-3yl thio)acetate (1) (1.05,0.003mole) with hydrazine hydrate (0.15 g,0.003mole) in 30ml absolute ethanol .then refluxed for (7-12) hrs.The precipitated solid was collected and recrystallized from ethanol. Table (1)

Preparation of Schiff bases (7,8)

To a stirring solution of compound(6)(2.7g,0.01mole)in absolute ethanol (15ml),an appropriate different aldehyde (0.01mole)was added with drops of glacial acetic acid, and then the mixture was refluxed 6hrs.Cooled at room temperature the precipitate was filtered and recrystallized from ethanol. Table (1)

Preparation of thiazolidenones (9,10)

A mixture of compound of Schiff bases(9 or10)(0.02mole)and 2-mercapto acetic acid (0.26ml,0.04mole)in dry benzene (30mL) was refluxed for 10hrs.The mixture was concentrated and recrystallized from methanol Table 1

Preparation of 2-(5,6diphenyl,1,2,4-triazine-3ylthio)-N-phenyl hydrazinecarbothioamide (11).

A mixture of compound(6)(3.37 g,0.01mole) and phenyl iso thiocyanate (1.31ml,0.01mole),in absolute ethanol (20ml) was refluxed for 3hrs. The solid product was filtered and recrystallized from ethanol. Table 1

Preparation of 2-(5,6 diphenyl -1,2,4-triazine-3ylthio)-N-(4-oxo-3-phenylthiazolidine-2-ylidene) aceto hydrazide (12).

Ethyl chloro acetate (0.49,0.004mole)was added dropwise to a stirring solution of compound(11) (1.89g,0.004mole)and anhydrous sodium acetate(0.004mole)in (20mL) absolute ethanol .The reaction mixture was refluxed for 6hrs.,the solid product was filtered and recrystallized from ethanol. Table 1

Preparation 2-(5,6 diphenyl -1,2,4-triazine-3-ylthio) acetic acid (13).

To (2.6 g, 0.01 mole)of 5,6-diphenyl -1,2,4-triazine-3-thiol in 20 ml of absolute ethanol ,(0.56, 0.01 mole) of KOH was added followed by (0.095 g, 0.01 mole) of mono chloro acetic acid . The reaction mixture was heated under reflux for 8 hrs., the hot solution was evaporated under reduced pressure ,the solid was filtered washed with cold distilled water and recrystallization from ethanol. Table 1

Preparation of 2-((5,6diphenyl-1,2,4-triazine-3-ylthio)methyl-3-1H-benzimidazol) (14).

Compound (13) (3.23 g, 0.01 mole)was refluxed for 10 hrs., with o-phenylenediamine (1.08 g, 0.01 mole)in 4N-hydro chloric acid (20mL). The mixture was neutralized with ammonia to precipitated the compound (14), the product was filtered and recrystallized from ethanol . Table 1.
SCHEME I:

\[
\text{Ph} = \text{Ph} ; \quad \text{ClCH}_2\text{COOH} ; \quad \text{PhCNS} ; \quad \text{SCH}_2\text{COOH}
\]

\[
\text{Ph} = \text{Ph} ; \quad \text{ClCH}_2\text{COOCH}_3\text{H}_3 ; \quad \text{PhCOCHBr}_{2} ; \quad \text{HSCH}_2\text{COOH}
\]

\[
\text{Ph} = \text{Ph} ; \quad \text{ClCH}_2\text{COOC}_2\text{H}_5 ; \quad \text{ClCH}_2\text{COOH}
\]
Results and DISCUSSION

New derivatives of 5,6-diphenyl-1,2,4-triazine-3-thiol containing another heterocyclic moiety were prepared following the reaction sequence depicted scheme I. Reaction 5,6 diphenyl-1,2,4-triazine-3-thiol with ethyl chloroacetate to form ethyl 2-(5,6 diphenyl-1,2,4-triazine-3-ythio) acetate (1), the FT-IR spectrum figure (1), show the appearance carbonyl of ester C=O 1730 cm$^{-1}$ (table 1), $^1$H-NMR(DMSO$_d_6$) ppm of compound (1): 1.05(t, 3H, CH$_2$C$_3$H$_3$), 4.15(s, 2H, CH$_2$CH$_3$), 4.31(s, 2H, SCH$_2$) 7.7-7.8 CH aromatic protons (table 2), then condensation compound (1) with thiourea or urea to afford compound (2,3), the FT-IR spectra show disappearance carbonyl of ester and appearance the CONH stretching band at (1683,1678) cm$^{-1}$ respectively (table 1), $^1$H-NMR(DMSO$_d_6$) ppm of compound (2): 4.0(s,2H,SCH$_2$), 7.7-7.9 CH aromatic protons, 8.0 (s,1H,NH)$_2$, 9.53(s,2H,NH) (table 2). Reaction compound (2,3) with bromo phenacyl bromide afforded compound (4,5), FT-IR spectra show the appearance carbonyl of amide (1672,1681) cm$^{-1}$ (table 1). Condensation ethyl 2-(5,6 diphenyl-1,2,4-triazine-3yl thio) acetate (1) with hydrazine hydrat to afforded 2(5,6di phenyl-1,2,4-triazine-3ylthio)aceto hydrazide (6), FT-IR spectrum figure(3), show the disappearance carbonyl of ester and appearance carbonyl of amide CONH 1660 cm$^{-1}$ (table 1), $^1$H-NMR(DMSO$_d_6$) ppm of compound 6: 4.0(s,2H,SCH$_2$), 4.22(d,2H,NHNH$_2$), 7.3-7.9 CH aromatic protons, 9.52(s,1H,NH$_2$) (table 2). Condensation hydrazide (6) with aromatic aldehydes to give (7,8) in absolute ethanol, the formation of these Schiff bases was indicated by the presence in their FT-IR spectra which show azomethine CH=N stretching at (1623-1628) cm$^{-1}$, treatment of Schiff bases (7,8) with 2-mercaptoacetic acid in dry benzene gave thiazolidenone derivatives (9,10) structure of these compounds were confirmed by the presence of C=O stretching band at (1720-1718) cm$^{-1}$ due to thiazolidinone ring (table 1). Treatment compound (6) with phenyl isothiocyanate afforded the corresponding thiourea-carbazide (11), the FT-IR spectra show the appearance C=S stretching band at 1272 cm$^{-1}$ and NH stretching band at 3296 cm$^{-1}$ (table 1), $^1$H-NMR(DMSO$_d_6$) ppm of compound 11 : 2.12(s,1H,CONNH$_2$), 7.3-7.7 CH aromatic protons, 10.08(s,1H,NH$_2$), 12.52(s,1H,CONH) (table 2). Refluxing of compound (11) with ethyl chloroacetate afforded 4-thioazolidone derivatives (12) which was confirmed by the presence of C=O stretching band at 1695 cm$^{-1}$ and C=N stretching band 1634 cm$^{-1}$ (table 1). Condensation of 5,6 diphenyl-1,2,4-triazine-3-thiol with mono chloro acetic acid afforded compound (13), FT-IR show the 3500 cm$^{-1}$ band of OH ,carbonyl of acid 1695 cm$^{-1}$, 603 cm$^{-1}$ band of C-S table 1, treatment compound (13) with o-phenylene diamine afforded compound (14). FT-IR show the appearance stretching band of NH 3306 cm$^{-1}$, 1620 C=N table 1.
### TABLE 1: PHYSICAL PROPERTIES AND SPECTRAL DATA OF COMPOUNDS

<table>
<thead>
<tr>
<th>NO</th>
<th>formula</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Color</th>
<th>Recrystallization Solvent</th>
<th>Infrared data cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₁₉H₁₇N₅O₂S</td>
<td>223-225</td>
<td>66</td>
<td>White</td>
<td>Chloroform</td>
<td>1730 C=O ester, 2997-2922 CH aliph, 3065 C-H arom., 1612 C=N, 1589 C=C arom., 671 C-S</td>
</tr>
<tr>
<td>2</td>
<td>C₁₈H₁₅N₅OS₂</td>
<td>166-168</td>
<td>60</td>
<td>White</td>
<td>Ethanol</td>
<td>1678 C=ONH, 2924 C-H aliph, 3039 C-H arom., 3412-3398NH₂, 610 C-S</td>
</tr>
<tr>
<td>3</td>
<td>C₁₈H₁₅N₅O₂S</td>
<td>190-192</td>
<td>55</td>
<td>White</td>
<td>Ethanol</td>
<td>1683 C=ONH, 2987 C-H aliph., 3062 C-H arom., 3310, 3248 NH₂, 603 C-S</td>
</tr>
<tr>
<td>4</td>
<td>C₂₆H₁₈BrN₅O₂S</td>
<td>210-212</td>
<td>60</td>
<td>Yellow</td>
<td>Ethyl acetate</td>
<td>1681 C=O amide, 2978 C-H aliph., 3045 C-H arom., 1649 C=N, 1597 C=C</td>
</tr>
<tr>
<td>5</td>
<td>C₂₆H₁₈BrN₅O₂S</td>
<td>222-224</td>
<td>65</td>
<td>Brown</td>
<td>Ethyl acetate</td>
<td>1672 C=O amide, 2931-2810 C-H aliph., 3021 C-H arom., 1638 C=N, 1554 C=C</td>
</tr>
<tr>
<td>6</td>
<td>C₁₇H₁₃N₅OS</td>
<td>198-200</td>
<td>70</td>
<td>White</td>
<td>Ethanol</td>
<td>1660 C=O amide, 3269-3232 N-H₂, 1595 C=C, 1616 C=N</td>
</tr>
<tr>
<td>7</td>
<td>C₂₄H₁₉ClN₅OS</td>
<td>165-167</td>
<td>75</td>
<td>Orange</td>
<td>Ethanol</td>
<td>3308 N-H, 3026 C-H arom., 1628 CH=N, 1006 C-Cl, 612 C-S</td>
</tr>
<tr>
<td>8</td>
<td>C₂₄H₁₉BrN₅OS</td>
<td>178-180</td>
<td>77</td>
<td>Orange</td>
<td>Ethanol</td>
<td>3184 N-H, 3024 C-H arom., 1623 CH=N, 610 C-Br</td>
</tr>
<tr>
<td>9</td>
<td>C₂₆H₂₀ClN₅O₂S</td>
<td>214-216</td>
<td>65</td>
<td>Dark yellow</td>
<td>Methanol</td>
<td>3290 N-H, 3093 C-H arom., 2895 C-H aliph., 1720 C=O, 1016 C-Cl</td>
</tr>
<tr>
<td>10</td>
<td>C₂₆H₂₀BrN₅O₂S</td>
<td>224-226</td>
<td>60</td>
<td>Yellow</td>
<td>Methanol</td>
<td>3311 N-H, 3020 C-H arom., 2909 C-H aliph., 1718 C=O, 643 C-Br, 1631 C=N</td>
</tr>
<tr>
<td>11</td>
<td>C₂₄H₂₀N₆OS₂</td>
<td>200-202</td>
<td>60</td>
<td>Brown</td>
<td>Ethanol</td>
<td>3296-3180 N-H, 3080 C-H arom., 1272 C=S</td>
</tr>
<tr>
<td>12</td>
<td>C₂₆H₂₀N₆O₂S</td>
<td>220-222</td>
<td>65</td>
<td>Brown</td>
<td>Ethanol</td>
<td>1695 C=O, 3210 N-H, 2920 C-H aliph., 1634 C=N</td>
</tr>
<tr>
<td>13</td>
<td>C₁₇H₁₃N₅O₂S</td>
<td>121-123</td>
<td>60</td>
<td>Brown</td>
<td>Ethanol</td>
<td>3500 OH, 3080 C-H arom., 1695 CO, 608 C-S</td>
</tr>
<tr>
<td>14</td>
<td>C₂₃H₁₇N₅S</td>
<td>230-232</td>
<td>69</td>
<td>Yellow</td>
<td>Ethanol</td>
<td>3377, 3306 NH, 3051 C-H arom., 2960 C-H aliph., 1620 C=N</td>
</tr>
</tbody>
</table>
TABLE 2:
CHEMICAL SCHIFF'S $^1H$-NMR SPECTRA.

<table>
<thead>
<tr>
<th>No.</th>
<th>$^1H$-NMR (DMSO-d$_6$)δ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.05(t,3H,CH$_2$CH$_3$), 4.15(s,2H,CH$_2$CH$_3$), 4.31(s,2H,SCH$_2$), 7.7-7.8 CH aromatic protons</td>
</tr>
<tr>
<td>2</td>
<td>4.0(s,2H,SCH$_2$), 7.7-7.9 CH aromatic protons, 8.0 (s,1H,NH)$_2$, 9.53(s,2H,NH$_2$)</td>
</tr>
<tr>
<td>6</td>
<td>4.0(s,2H,SCH$_2$), 4.22(d,2H,NH$_2$), 7.3-7.9 CH aromatic protons, 9.52(s,1H,NH$_2$)</td>
</tr>
<tr>
<td>11</td>
<td>2.12(s,1H,CNH$^2$), 7.3-7.7 CH aromatic protons, 10.68(s,1H,NH$_2$), 12.52(s,1H,CNH$^2$)</td>
</tr>
</tbody>
</table>

Figure 1: FT-IR Spectrum of compound (1)

Figure 2: $^1H$-NMR Spectrum of compound (1)

Figure 3: FT-IR Spectrum of compound (6)

Figure 4: $^1H$-NMR Spectrum of compound (6)
REFERENCES:


