Synthesis of Some Heterocyclic Compounds derived from 2-mercapto pyrimidine

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Abstract:
In this work 2-hydrazone pyrimidine (1) was prepared from 2-mercapto pyrimidine with hydrazine hydrate.

Treatment of (1) with active methylene compounds gave 2-(3,5-dimethyl -1 H – Pyrazole-1-yl) pyrimidine , whereas the reaction of (1) with carboxylic anhydride namely maleic anhydride or 1,2,3,6-tetra hydro phthalic anhydride yielded 1-Pyrimidine-2-yl-1,2-dihydro pyridazine-3,6-dione (3) and 2 – Pyrimidin -2-yl -2,3,4 a ,5,8 a – hexahydro phthalazaine 1,4 – dione (4) .

Reaction of (1) with phenyl isothiocyanate and ethyl chloro acetate afforded 3-Phenyl-1,3-thiazolidine-2,4-dione-2( pyrimidine -2- yl hydrazone (6) Azomethine (7-10) were prepared through condensation of (1) with aromatic aldehydes or ketones, then compounds (7-9) are converted into a number of tetrazole derivatives (11-13).

Treatment of (1) with acetic acid afforded the derivative (14).

The reaction of 2-mercapto pyrimidine with ethyl chloro acetate afforded (15), whereas the reaction of (15) with thiosemicarbazide and 4% sodium hydroxide leads to ring closure giving 1,2,4 triazole derivative (17).

Moreover the reaction of 2-mercapto pyrimidine with chloro acetic acid gave (18) followed by refluxing (18) with o- amino aniline to give the benzimidazole derivative (19). the structure of these compounds were characterized by FR-IR, UV spectra and some of them were characterized by element analysis.

Key words: 2-mercapto pyrimidine, pyrazol, 1,2,4-triazole, Pyridazione.

Introduction:
Pyrazole derivatives have attracted particular interests during the last twenty five years due to the use of such ring system as the core structure in many drug substances, covering wide range of pharmacological applications [1,2].

Synthetic pyridazinone derivatives as important scaffolds in drug discovery, with many of their analog being used in the treatment of various human pathological states [3]. 4-Thiazolidinone derivatives play a vital role owing to their wide range of biological activity and industrial importance as stabilizers for polymeric materials [4,5].

In recent years, derivatives of Schiff bases, 1,2,4-triazole and tetrazole have been found to exhibit some biological and pharmaceutical properties [6], antibacterial[7] antihistaminic[8], antifungical [9] anti-inflammatory [10]. Benzimidazole and its derivatives have attracted researcher's interest in the fields of bioorganic and medical chemistry to their significant antifungal, antibacterial and insecticidal properties [11].

We now report on the synthesis of compounds derived from 2-mercapto pyrimidine containing pyrazole, Pyridazione thiazolidinone, tetrazole.
triazole and benzimidazole moieties, with the purpose of investigating in the future their possible antibacterial and antifungal activities.

Result and Discussion:
The reaction sequence for titled compounds is outlined in Schemes 1, 2.

(1) which was prepared by the reaction of 2-mercapto pyrimidine with hydrazine hydrate. The starting material for the synthesis of targeted compounds is 2-hydrazino pyrimidine.

Treatment of (1) with active methylene compound such as acetyl acetone produced pyrazolo derivative (2).

The structure of (2) was confirmed by their FTIR and UV spectra through the appearance of the band at 1371 cm⁻¹ for CH₃ bending vibration and disappearance of the NH₂ and NH stretching bands in (2) .
Treatment of (1) with carboxylic anhydrides, e.g. maleic anhydride and 1,2,3,6-tetrahydrophthalic anhydride gave 1-(Pyrimidine-2-yl)-1,2-dihydro pyridazin-3,6-dione (3) and compound (4).

FTIR spectrum of (3) shows broad bands at 3450 cm\(^{-1}\) and 3221 cm\(^{-1}\) which where assignable to (NH) stretching vibrations.

The stretching vibration band at 1716 cm\(^{-1}\) was due to \(\nu(C=O)\) moiety of pyridazine ring while the \((C=O)\) stretching of amide 1624 cm\(^{-1}\).

We can say that compounds (3) or (4) can be exist in two tautomeric forms, keto and enol forms.

The mechanism of reaction is shown in scheme (3).

Scheme (2)
Reaction between (1) and phenyl isothiocyanate afforded the corresponding thiosemicarbazide 5 in moderate yield.

The FTIR spectra of (5) display (C=S) stretching band at 1255 cm\(^{-1}\) and (NH) stretching band at 3227 cm\(^{-1}\).

Refluxing of compound (5) with ethylchloroacetate and anhydrous sodium acetate in absolute ethanol for six hours afforded 4- thioazolidone (6). The structure of (6) was confirmed by the presence of (C=O) stretching band at 1720 cm\(^{-1}\) and (C=N) stretching band at 1643 cm\(^{-1}\).

Condensation of (1) with aryl aldehydes or Isatin in absolute ethanol gave the Schiff’s bases (7-10).

The formation of these Schiff bases was indicated by the presence in their FTIR spectra of azomethine (C=N) stretching band at 1600-1640 cm\(^{-1}\), combined with the disappearance of NH\(_2\) stretching band.

Moreover, treatment of Schiff’s bases (7-9) with (NaN\(_3\)) produced tetrazole derivatives (10-13).

Structures of these compound, were confirmed by the disappearance of band at (1600-1640) cm\(^{-1}\), attributed to (C=N) (imine group) stretching frequency which was agood evidence for the success of this step of reaction .Beside this , FTIR spectra of these compounds were devoid of a strong band at (2160-2120) cm\(^{-1}\) attributed to stretching frequency of azide group .

A band at the range (1136-1087) cm\(^{-1}\) was due to tetrazole ring[12]. Treatment of (1) with acetic acid gave 5- methyl -1,2,4-triazolo-[4,3-a]-Pyrimidine (14).

The FTIR spectra of (14) showed a band at 1380 cm\(^{-1}\) for the (C-H) in (CH\(_3\)), in addition to the band at 1635 cm\(^{-1}\) for (C=N) stretch.

On the other hand the reaction of starting material 2-mercapto pyrimidine with ethylchloroacetate afforded (15), which displayed (C=O) stretching band at 1737 cm\(^{-1}\).

Treatment of (15) with powdered thiosemicarbazide in dry benzene afforded the acylthiosemicarbazide (16). Which upon ring closure with 4% NaOH gave 5-(pyrimidine -2- yl thio methyl)-4H-1,2,4-triazole -3- thiol (17)[13], which exists in a tautomeric thiol –thione equilibrium as indicated by the C=S stretching band at 1180 cm\(^{-1}\) and S-H stretch at 2550 cm\(^{-1}\) [14].

In order to synthesize pyrimidine -2-yl-mercapto-acetic acid (18), the starting material 2-mercapto pyrimidine was react with mono-Chloro acetic acid. Condensation of compound (18) with o-phenylene diamine yielded the benzimidiazole derivative (19). Structure of compound (19) was confirmed by FTIR spectra data which showed the disappearance of bands at 3400 cm\(^{-1}\) and 1718 cm\(^{-1}\) attributed to (OH) and (C=O) of carboxylic acid in compound (18). Elemental analysis proved the structural formula for some compounds as well as the purity of each compounds.

**Material and Methods:**

**General**

Melting points were determined in open capillary tubes on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra discs (KBr) were recorded with a Shimadzu FTIR-8400, UV spectra were recorded on a Shimadzu 160A UV/VIS spectrophotometer using absolute ethanol as solvent. Element analysis were done on EURO EA instrument in Al - Mustansiriya University. Starting chemical compounds were obtained from Fluka or BDH.

**Prepatration of 2-hydrazino pyrimidine (1):**

A mixture of 2-mercapto pyrimidine (0.01 mole,1.12g) and hydrazine hydrate (10 ml) was refluxed for
3 hours, ethanol (15 ml) was added and refluxed for 4 hours. The separated precipitate was filtered and washed with cold water and recrystallized from ethanol.

**Preparation of 2-(3,5-dimethyl-1H-Pyrazol-1-yl)pyrimidine (2):**

To a solution of Compound (1) (0.002 mole, 0.22 g) in absolute ethanol (20 ml) was added acetyl acetone (0.002 mole, 0.2 ml). The reaction mixture was refluxed for 6 hours. After concentration and cooling, the solid product that formed was filtered and recrystallized from ethanol. Compound (2), Calc. For C<sub>9</sub>H<sub>10</sub>N<sub>4</sub> (%): C, 62.20; H, 5.75; N, 32.16; found % : C, 62.38; H, 5.58; N, 31.94.

**General procedure for preparation of 1-pyrimidine -2-yl 1,2-dihydropyrazidine-3,6-dione (3) and 2-pyrimidine -2-yl-2,3,4a,5,8, 8a-hexa hydro phthalazine-1,4-dione(4)[15]**

Maleic anhydride or 1,2,3,6-tetrahydro phthalic anhydride (0.01 mole) in (30 ml) acetic acid was added to hydrazide (1) (0.01 mole, 1.1 g) and the reaction was refluxed for (7 hours). Then the mixture was poured on crushed ice, the formed solid product was filtered off and recrystallized from pet. ether (40-60°C).

**Preparation of N- Phenyl -2-Pyrimidine-2-yl-hydrazine carbothio -amide (5).**

A mixture of Compound (1) (0.01 mole, 1.1 g) and phenyl isothiocyanate (0.011 mole, 1.31 ml) in absolute ethanol (20 ml) was refluxed for 3 hours and cooled. The solid product was filtered and recrystallized from ethanol. Compound (5), Calculated For C<sub>11</sub>H<sub>11</sub>N<sub>5</sub>S (%): C, 53.87; H, 4.48; N, 28.57; S, 13.06; Found (%) : C, 53.99; H, 4.61; N, 28.60; S, 12.80.

**Preparation of 3- phenyl -1,3-thiazolidine -2,4-dione-2- (Pyrimidine-2-yl-hydrazone) (6)**

Ethyl chloroacetate (0.01 mole, 0.9 g) was added dropwise to a stirred solution of compound (5) (0.01 mole, 2.4 g) and anhydrous sodium acetate (0.01 mole) in (20 ml) absolute ethanol. The reaction mixture was refluxed for 6 hours. The solid product was filtered and recrystallized from ethanol.

**Preparation of Compounds (7-10)**

A mixture of Compound (1) (0.002 mole, 0.22 g) and the corresponding aryl aldehyde or Isatin (0.002 mole) in absolute ethanol (20 ml) was refluxed for (3 hours) and cooled. The solid product was filtered and recrystallized from ethanol.

**Preparation of 2-[5-Substitutedtetrazol-1-yl]-Pyrimidine(11-13)**

A mixture of (0.002 mole) of appropriate Schiff base (7-9), dry acetone (15 ml) and sodium azide (0.002 mole, 0.13 g) was heated on a water bath, the temperature of the water bath was controlled between (50-55°C). The end of the reaction was checked by TLC which showed the disappearance of the starting material.

**Preparation of 5- methyl-1,2,4-triazole[4,3-a]-pyrimidine (14).**

The solution of compound (1) (0.003 mole, 0.33 g) in glyacial acetic acid (10 ml) was heated under vacuum as much as possible and the mixture was poured onto ice-cold water. The solid was filtered, washed with water and recrystallized from ethyl acetate. Compound (14), Calc. for C<sub>6</sub>H<sub>5</sub>N<sub>4</sub> (%): C, 53.73; H, 4.47; N, 41.79; Found (%): C, 53.85; H, 4.10; N, 42.05.
Preparation of Ethyl –(pyrimidine-2-thio)acetate (15)

Ethyl chloroacetate (0.01 mole, 0.95g) was added dropwise to a stirred solution of 2- mercaptopyrimidine (0.01 mole, 1.12g) and KOH (0.56 gm, 0.01 mole) in (20 ml) absolute ethanol. The reaction was mixture refluxed for (5 hours). The solid was filtered, washed with water and recrystallized from chloroform. Compound (15):

Calc. for C₈H₁₀N₂O₂S (%): C, 48.48; H, 5.05; N, 14.14; S, 16.16; found (%): C, 48.30; H, 4.90; N, 13.90; S, 16.00.

Preparation of 2-[(pyrimidine-2-yl-thio)acetyl]hydrazinecarbothioamide (16)

To solution of compound (16) (0.01 mole, 1.71g) in absolute ethanol (20 ml) was added thiosemicarbazide (0.01 mole, 0.92g). The mixture was refluxed for 4 hour and after cooling the precipitate was filtered and recrystallized from ethanol – water.

Preparation of 5-(pyrimidine-2-yl-thiomethyl)-4H-1,2,4-triazole-3-thio (17)

A stirred mixture of compound (17) (0.03 mole, 0.633g) and aqueous sodium hydroxide (4%, 10 ml) was refluxed for (3 hours). The mixture was acidified with dil. HCl and the precipitate was collected crystallized from ethanol.

Preparation of pyrimidine-2-yl-mercapto acetic acid (18)

To (0.01 mole, 1.12g) of 2-mercapto pyrimidine in (20 ml) of ethanol (0.01 mole) of KOH was added followed by (0.01 mole, 0.95g) of monochloroacetic acid. The reaction mixture was heated under reflux for (8 hours). The hot solution was evaporated under reduced pressure. The solid was filtered washed with cold distilled water. and recrystallized from ethanol.

Preparation of 2-(1H-benzimidazol-2yl-thiomethyl)pyrimidine (19)

Compound (18) (0.01 mole, 1.7g) was refluxed for 12 hours with o-phenylene diamine (0.01 mole, 1.08g) in 4N hydrochloric acid (20 ml). The reaction mixture was cooled and then neutralized with ammonia to precipitate benzimidazole. The crude product was recrystallized from ethanol.

All physical constant for these compounds were reported in table-1.
Table 1. physical constants and spectroscopic data for compounds.

<table>
<thead>
<tr>
<th>Com. No.</th>
<th>Formula</th>
<th>MP, °C</th>
<th>Yield %</th>
<th>UV, λ max (E1%1cm)</th>
<th>Infrared data (ν, cm⁻¹) (KBr disc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₇H₈N₄</td>
<td>226-228</td>
<td>75</td>
<td>250, 339</td>
<td>3290, 3185 (N-H), 3084 (C-H₉₅), 1560 (C=O), 1630 (C=N);</td>
</tr>
<tr>
<td>2</td>
<td>C₆H₁₀N₄</td>
<td>110-112</td>
<td>60</td>
<td>285, 320, 389</td>
<td>3030 (C-H₉₅), 2926 (C-H), 1614 (C=N), 1568 (C=C);</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₈N₄O₂</td>
<td>188-190</td>
<td>50</td>
<td>204, 245</td>
<td>3450 (OH), 3221 (NH), 2939 (C-H), 1716 (C=O) 1624 (C=O amide)</td>
</tr>
<tr>
<td>4</td>
<td>C₁₂H₁₂N₆O₂</td>
<td>220-222</td>
<td>65</td>
<td>240, 380</td>
<td>3240 (N-H), 2928 (C=H₆), 1697 (C=O), 1654 (C=O amide)</td>
</tr>
<tr>
<td>5</td>
<td>C₁₁H₁₃N₅S</td>
<td>200-202</td>
<td>72</td>
<td>204, 262, 367</td>
<td>3227, 3186 (N-H), 3030 (C-H₆), 1255 (C=O), 1629 (C=N), 1554 (C=C)</td>
</tr>
<tr>
<td>6</td>
<td>C₁₃H₁₄N₆OS</td>
<td>226-228</td>
<td>65</td>
<td>202, 265, 315</td>
<td>3458 (N-H), 3084 (C=H₆), 1720 (C=O amide), 1643 (C=N), 676 (C-S-C);</td>
</tr>
<tr>
<td>7</td>
<td>C₁₁H₈N₄OCl</td>
<td>254-256</td>
<td>82</td>
<td>204, 260, 290</td>
<td>3309 (OH), 3105 (NH), 3020 (C=H₆), 1631 (C=N=O sym.), 1572 (C=N=O asym.), 820 (C=Cl)</td>
</tr>
<tr>
<td>8</td>
<td>C₁₁H₈N₄O₂</td>
<td>248-250</td>
<td>83</td>
<td>206, 270, 288</td>
<td>3281 (NH), 1640 (C=N=O), 1581 (C=N=O asym.), 1336 (NO₂ sym.), 1510 (NO₂ asym.)</td>
</tr>
<tr>
<td>9</td>
<td>C₁₁H₁₄N₅O</td>
<td>270-273</td>
<td>80</td>
<td>208, 287, 302</td>
<td>3320 (OH), 3211 (NH), 3090 (C=H₆), 1646 (C=N=O asym.), 1590 (C=N=O asym.)</td>
</tr>
<tr>
<td>10</td>
<td>C₁₃H₁₄N₅O</td>
<td>202-204</td>
<td>79</td>
<td>210, 260, 300</td>
<td>3319, 3211 (NH), 3100 (C=H₆), 1685 (C=O amide), 1645 (C=O)</td>
</tr>
<tr>
<td>11</td>
<td>C₁₁H₈N₄OCl</td>
<td>200-202</td>
<td>65</td>
<td>204, 249, 396</td>
<td>3300-3000 (OH), 3281 (NH), 1610 (C=N) 1095, 1136 (tetrazole), 814 (C=Cl)</td>
</tr>
<tr>
<td>12</td>
<td>C₁₁H₈N₄O₂</td>
<td>234-236</td>
<td>60</td>
<td>204, 240, 310</td>
<td>3390 (NH), 1626 (C=N), 1342 (NO₂ sym.), 1519 (NO₂ asym.), 1012, 1105 (tetrazole)</td>
</tr>
<tr>
<td>13</td>
<td>C₁₁H₈N₄O</td>
<td>228-230</td>
<td>58</td>
<td>202, 255</td>
<td>3269 (OH), 3260 (NH), 1635 (C=N), 1157, 1087 (tetrazole)</td>
</tr>
<tr>
<td>14</td>
<td>C₁₂H₆N₄</td>
<td>229-231</td>
<td>78</td>
<td>204, 260</td>
<td>3070 (C=H₆), 2988 (C=H₆), 1635 (C=N), 1590 (C=C), 1380 (CH₂ bend.)</td>
</tr>
<tr>
<td>15</td>
<td>C₁₀H₁₀N₄S₂</td>
<td>196-198</td>
<td>73</td>
<td>204, 254, 312</td>
<td>3098 (C=H₆), 2978 (C=H₆), 1737 (C=O amide), 1250 (C=O), 640 (C=S)</td>
</tr>
<tr>
<td>16</td>
<td>C₁₂H₈N₄OS</td>
<td>210-212</td>
<td>67</td>
<td>230, 375</td>
<td>3379, 3263 (NH₂), 3153 (NH), 2997 (C=H₆), 1660 (C=O), 1300, 1269, 1109 (NH=CH₂)</td>
</tr>
<tr>
<td>17</td>
<td>C₁₂H₈N₄S₂</td>
<td>211-213</td>
<td>60</td>
<td>202, 250, 360</td>
<td>3160 (NH), 2550 (SH), 1640 (C=N), 1180 (C=S)</td>
</tr>
<tr>
<td>18</td>
<td>C₁₂H₈N₄O₂S</td>
<td>250-252</td>
<td>72</td>
<td>220, 380</td>
<td>3400-2500 (OH), 3030 (C=H₆), 2930 (C=H₆), 1718 (C=O), 1565 (C=N)</td>
</tr>
<tr>
<td>19</td>
<td>C₁₂H₁₀N₆S</td>
<td>240-242</td>
<td>67</td>
<td>204, 387</td>
<td>3180 (NH), 3064 (C=H₆), 2982 (C=H), 1640 (C=N), 720 (C=S)</td>
</tr>
</tbody>
</table>

References:


تحضير بعض المركبات الحلقيّة الغير المتجانسة المشتقة من 2-مركبتو بريميدین

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الخلاصة
في هذا العمل حضرت 2-هايدرازو بريميدین (1) من 2-مركبتو بريميدین مع هايبرازين اللازمین وبمعاملة (1) مع المركبات الحاوية على مثلثي فعال 2-(3،5،7-تريازول-1-بلايبرازول-1-بلي) بريميدین. بينما تفاعل (1) مع الهيبرازين الكاربوكسيديلية مثل هايبرازين المالیك أو هايبرازين ماليك، الدفاع اعطت 1- هايبرازين-2-بلي-2-ثنائي بيردامازين-3،6 ثنائي اون (3، و 2-بريميدین-2-بلي-2، 3، 4، 5، 6، 7، 8، 9، 10 هايبرازين-1، 4، 3، 6، 4، 1-هدي احمد حسن
ناهدة عبد الله جنیل

مرکبات آزمایشی (7-10) حضرت از مجموع کانکفاکت (1) مع الالدی‌هیدرز آرمانیه یا کیتنو، ثم المركبات (9-7) تحول وردیاً إلى عدد من مشتقات التترازول (11-13). معاملة (1) مع حمض الخليک اعطاء المشتق (14). وتفاعل 2-مركبتو بريميدین مع الیل کلوروسائنتی اعطی (15) مع ثایوسیکاریزادوی میکین کیستن ای (17) تفاعل 2-مركبو بريميدين مع حامض کلورو استیک اعطی (18) يتعین تعیین (18) مع اورتو- امیدادوین لبعض المشتق بتراپازول (19) تتم تشریح المركبات المحضرة بواسطة الاستعاقة تحت الحمراء فرعیة بتحويلات فوریر والاشعة فوق البینسجیة وكذلك بعض منها تم تشریحها باستخدام التحلیل الدقيق للعناصر.