Synthesis of five membered ring hetero cyclic compounds derived from methyl-6- methyl-2- oxo-4- substituted 1,2,3,4-tetrahydro pyrimidine-5- carboxylate

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Abstract

In this paper the synthesis of methyl-6- methyl-2-oxo-4-substituted phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1-3) were synthesised from substituted benzaldehyde, urea and methyl acetoacetate, substituted pyrimidine (1-3) were treated with hydrazine hydrate in butanol to give acid hydrazide (4-6), which were converted to hydrazones (7-12) by their reaction with substituted benzaldehyde. Cyclization of hydrazones (7-12) with lead dioxide in glacial acetic acid gave substituted
Synthesis of five membered ring heterocyclic compounds derived …

1,3,4-oxadiazole (13-18). Hydrazide (4-6) were treated with ammonium thiocyanate in ethanol and hydrochloric acid to give substituted thiosemicarbazides(19-21). Reaction of thiosemicarbazide (19-21) with 4% sodium hydroxide or with concentrated sulfuric acid gave substituted 1,2,4- (4H) - triazole (22-24) and 1,3,4- thiadiazole (25-27) respectively. The structure of the synthesized compounds, were confirmed by IR, UV and physical methods.

Introduction

It is well known that pyrimidine derivatives possess biological activities specially as antiviral , antimicrobial (1-4) and act as antitumour agent (5), antibacterial (6, 7) and anti-lukemic (8). The synthesis and biological activity of thienopyrimidine derivatives from aromatic and heteroaromatic compounds and the preparation of various condensed pyrimidine was studied(9). The synthesis of 5,6,7,8-tetrahydro [1] benzothieno[2,3-d] pyrimidine -4-(3H) - one (2) was achieved from 2-amino - 4,5- dihydro - 4H- cyclopenta [b] thiophene-3-carboxamide (1) by its reaction with formamide(10).

\[
\begin{align*}
\text{(1)} & \hspace{2cm} \text{(2)} \\
\end{align*}
\]

The pyrimidine derivative (4) was obtained from the reaction of ethyl - 2- amino- 4,5,6,7-tetra hydro- benzothiophene -3-carboxylate (3) with excess formamide(11).

\[
\begin{align*}
\text{(3)} & \hspace{2cm} \text{(4)} \\
\end{align*}
\]

S-glycosyl pyrimidine and condensed pyrimidine derivatives were synthesized from isothiocyanate and acrylate(12). Some heterocyclic compounds containing pyrimidino-pyrimidine moiety as
compound(5) have been synthesized, and these compounds showed antibacterial activity against gram – positive and negative species\(^{(13)}\)

\[
\begin{align*}
\text{R} &= \text{H, CH}_3, \text{Cl, OMe, NO}_2 \\
\end{align*}
\]

Pyrimidine derivatives as pyrido[2,3-d]pyrimidin-4-(3H) – one \((6)\) was synthesized\(^{(14)}\) where as condensation of chalcone with thiourea in presence of potassium hydroxide gave 1,6-Dihydropyrimidine-2-thiol which show antibacterial activity \(^{(15)}\).

\[
\begin{align*}
\text{R} &= \text{NH}_2, \text{H, OH, CH}_3 \\
\end{align*}
\]

3 – cyano -7- methyl – 4- oxo – 2 – (methyl thio)- 4H-pyrido[1,2-a] pyrimidine was synthesised from ethyl -2- cyano-3,3- bis (methyl thio) acrylate \(^{(16)}\). In this paper the synthesis of substituted tetrahydro-pyrimidines is reported.

**Experimental**

All chemicals were purchased from Flucka and BDH Chemical Ltd. The melting points were measured on an Electrothermal 9300 Engineering LTD and are uncorrected. IR spectra were recorded on
Infrared Spectrophotometer Model Tensor 27 ,Bruker Co.,Germany, using KBr discs . UV spectra were recorded on Shimadzu Double-Beam Spectrophotometer UV-210 A using ethanol as a solvent.

**Methyl -6- methyl -2- oxo -4- substituted phenyl -1,2,3,4- tetrahydropyrimidine -5- carboxylate (1-3)** (17):

To a mixture of urea (0.75g , 0.0125mole), substituted aldehyde (0.0185 mole), methyl acetoacetate (2.2g, 0.0185 mole) in ethanol (20ml), dilute hydrochloric (4 drops) was added. The mixture was heated at 70°C for 2h, ice cold water(100ml) was added and left for 24h. at room temperature, the solid was filtered and recrystallized from ethanol. Some of the physical data table (1)

**6-methyl -2- oxo - 4-substituted phenyl -1,2,3,4-tetrahydropyrimidine -5- carboxyhydrazide (4-6)** (18):

A mixture of compound (1-3) (0.00125 mole) in ethanol (40 ml), hydrazine hydrate (5 ml) was added then the mixture refluxed for 5h, the solvent was evaporated under reduced pressure to give compounds 4,6 as solid and 5 as oil compounds, compounds were recrystallized from ethanol-water. Some of the physical data table (1)

**Hydrazone (7-12)** (18):

To hydrazide (4-6)(0.011mole) in absolute ethanol (50 ml), substituted benzaldehyde (0.011 mole) in ethanol (25 ml) was added, the mixture refluxed for 5h, the precipitate was filtered and recrystallized from ethanol. Some of the physical data table (1)

**2- ( 4-methyl -6- substituted -2- one tetrahydroxyprimidin -5- yl ) 5- substituted 1, 3, 4-oxadiazole . (13-18)** (19):

Hydrazone (7-12) (0.005 mole) was added to glacial acetic acid (16ml) with stirring, lead oxide (1.24g, 0.005mole) was added as portions at 25°C the mixture was stirred for 1h. The reaction mixture was diluted with water (50 ml) and left for 24 h. the precipitate was filtered recrystallized from ethanol. Some of the physical data table (1)

**N-(2-amino-2-thioxethoxy)-4-(substituted phenyl)-6- methyl -2-oxo-1,2,3,4-tetrahydro pyridinidene-5-carboxamide (19-21)** (20):

A mixture of hydrazide (4-6)(0.011 mole), ammonium thiocyanate (2.7 g, 0.034 mole) concentrated hydrochloric acid (6 ml) in absolute ethanol (50 ml) was refluxed for 22h. Solvent was evaporated under reduced pressure and the residue was added to crushed ice with stirring to give solid product filtered and recrystallizid from ethanol - water. Some of the physical data table (1)

**4-( substituted phenyl) -5- (5-mercapto-4H-1,2,4-triazolo-3-yl)-6- methyl-3,4-dihydropyrimidin2-(1H)-one (22-24)** (21):

A mixture of thiosemicarbazide (19-21)(0.006 mole)in aqueous sodium hydroxide solution (4 % ,24ml) was refluxed for 3 h. The mixture then acidified with dilute hydrochloric acid to PH=6 with cooling , the
precipitate was filtered and recrystallized from ethanol. Some of the physical data table (1)

5-(5-amino-1,3,4-thiadiazol-2-yl)-4-(4-substitutedphenyl)-6-methyl-3,4-dihydropyrimidine-2-(1H)-one (25-27) (21):

A mixture of substituted thiosemicarbazide (19-21)(0.06 mole) and concentrated sulfuric acid (12 ml) was stirred at room temperature for 1h. then heated on water path at 90 °C for 2 h. the mixture was poured on a beaker containing crushed ice and nutralized with concentrated ammonium hydroxide with cooling the solid was filtered , washed with cold water dried and recrystallized from ethanol . Some of the physical data table (1).

Table (1) : physical data of compounds (1-27)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R</th>
<th>R'</th>
<th>m.p. °C</th>
<th>Molecular formula</th>
<th>Yield %</th>
<th>Color</th>
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<td>CH₃O</td>
<td></td>
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<td>C₁₄H₁₆N₂O₄</td>
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<tr>
<td>2</td>
<td>OH</td>
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<td>223-225</td>
<td>C₁₃H₁₄N₂O₄</td>
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<td>Cl</td>
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<td>NO₂</td>
<td>264-266</td>
<td>C₂₀H₁₉N₅O₅</td>
<td>71</td>
<td>Pale yellow</td>
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</table>
Synthesis of five membered ring heterocyclic compounds derived from ...
Synthesis of five membered ring heterocyclic compounds derived from substituted tetrahydropyrimidine (1-3) were synthesized and converted to substituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles (Scheme -2). Substituted benzaldehyde, was treated with urea and methyl acetoacetate to give tetrahydropyrimidine 1-3. The IR spectra shows absorption peaks at 1644, 3444, 3104, 2955 and 1730 cm\(^{-1}\) for (CO-amide), N-H, (C-H aromatic), (C-H aliphatic) and (C=O ester) respectively. The esters (1-3) were treated with hydrazine hydrate in butanol to give acid hydrazide, (4-6), the IR spectra show absorption at 1643-1646 cm\(^{-1}\) for (C=O) with disappearance of C=O esters absorption band at 1713-1730 cm\(^{-1}\). Acid hydrazide (4-6) were treated with substituted benzaldehyde to give hydrozone (7-12) which show absorption 1644-1681 cm\(^{-1}\) for(CO) 3257-3445-cm\(^{-1}\) for (N-H) compounds 8,10,12 show absorption at 1337-
Synthesis of five membered ring heterocyclic compounds derived …

1346, 1487-1525 cm\(^{-1}\) sym, and asym. for NO\(_2\). Substituted 1,3,4-oxadiazole (13-18) were synthesized from hydrazones (7-12) by their reaction with lead oxide in glacial acetic, the IR spectra show absorption at 1642-1700 (C=O), NO\(_2\) group appears at 1337-1346 cm\(^{-1}\) (sym. and asym.), the substituted thiosemicarbazides (19-21) were synthesized from hydrazide (4-6) by their reaction with ammonium thiocyanate -HCl in ethanol the IR spectra of compounds (19-21) show absorption at 1643-1649 cm\(^{-1}\) for (C=O amide) and 1180-1185 cm\(^{-1}\) for (C=S). The substituted thiosemicarbazides (19-21) were cyclized to substituted 1,2,4- triazoles (22-24) and to substituted 1,3,4- thiadiazole (25-27) by their reaction with 40% sodium hydroxide and with concentrated sulfuric acide respectively. The proposed mechanism of the cyclization of thiosemicarbazides (19-21) to thiadiazoles (25-27) as in scheme -1\(^{22}\)

![Scheme-1](image)

The IR of compounds (22-24) show absorption at 1638-1655 cm\(^{-1}\) for (C=N) and 1181-1218 cm\(^{-1}\) for (C=O). Compounds (25-27) showed absorption for (C=N) at 1631-1667 cm\(^{-1}\) and for (C=O at 1094-1129 cm\(^{-1}\). The thiadiazoles (25-27) show in absorption bonds for (C=S) at 1180-1185 cm\(^{-1}\) which found in compounds (19-21) Table(2).
Synthesis of five membered ring heterocyclic compounds derived …

Table (2): spectral data of compounds (1-27)

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<th>Comp. No.</th>
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<th>IR $\nu$ cm$^{-1}$, (KBr)</th>
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*N-CH₃ 2830*

*NO₂ 1346 sym. 1487asy. C-O-C (1027)*

*N-CH₃ (2802) C-O-C (1063)*

*NO₂ 1346, 1519asy. C-O-C (1040)*

*N-CH₃ 2890 C-O-C 1047*

*NO₂ 1337, 1486 C-O-C 1027*

*C=S 1183*

*C=S 1185*

*C=S 1180*

*C=N 1638 C=S 1218*
Synthesis of five membered ring hetero cyclic compounds derived …

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<td>1655</td>
<td>C-S</td>
<td>1129</td>
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</table>
Synthesis of five membered ring heterocyclic compounds derived …

\[
\begin{align*}
\text{C-H} + \text{NH}_2 - \text{C-NH}_2 + \text{CH}_3 - \text{C-CH}_2 - \text{C-OCH}_3 & \rightarrow \text{HN-CH}_3 \\
\text{O} & \text{O} \\
\text{N} \text{H} & \text{H} \\
\text{R} & \\
\text{O} & \text{C-CH}_3 \\
\end{align*}
\]

\((1 - 3)\)

\[
\begin{align*}
\text{NH}_2\text{NH}_2\text{H}_2\text{O} & \rightarrow \text{HN-CH}_3 \\
\text{BuOH} & \\
\text{O} & \text{O} \\
\text{N} \text{H} & \text{H} \\
\text{R} & \\
\text{O} & \text{C-CH}_3 \\
\end{align*}
\]

\((4 - 6)\)

\[
\begin{align*}
\text{HCl/EtOH} & \rightarrow \text{HN-CH}_3 \\
\text{NH}_4\text{SCN} & \\
\text{O} & \text{O} \\
\text{N} \text{H} & \text{H} \\
\text{R} & \\
\text{O} & \text{C-CH}_3 \\
\end{align*}
\]

\((7 - 12)\)

\[
\begin{align*}
\text{H}_2\text{SO}_4\text{Conc.} & \rightarrow \text{HN-CH}_3 \\
\text{4%NaOH} & \\
\text{O} & \text{O} \\
\text{N} \text{H} & \text{H} \\
\text{R} & \\
\text{O} & \text{C-CH}_3 \\
\end{align*}
\]

\((13 - 18)\)

\[
\begin{align*}
\text{PbO}_2 & \rightarrow \text{HN-CH}_3 \\
\text{CH}_3\text{COOH} & \\
\text{O} & \text{O} \\
\text{N} \text{H} & \text{H} \\
\text{R} & \\
\text{O} & \text{C-CH}_3 \\
\end{align*}
\]

\((19 - 21)\)

\[
\begin{align*}
\text{R CHO} & \rightarrow \text{HN-CH}_3 \\
\text{O} & \text{O} \\
\text{N} \text{H} & \text{H} \\
\text{R} & \\
\text{O} & \text{C-CH}_3 \\
\end{align*}
\]

\((7 - 12)\)

\[
\begin{align*}
\text{R}= & \text{CH}_3\text{O} - \text{C} - \text{CH} \\
\text{OH} & \text{R}=
\end{align*}
\]

\(\text{Scheme -2}\)
Synthesis of five membered ring heterocyclic compounds derived …

References

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