A One Step Synthesis of New 4-Aminopyrimidine Derivatives: Preparation of Tetrazolo- and s-Triazolopyrimidines

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Z. Naturforsch. 38b, 1686–1689 (1983); received June 13, 1983

Malononitrile, Urea Derivatives, Pyrimidines, Tetrazolopyrimidine, s-Triazolopyrimidine

2-Mercapto-4-amino-5-cyano-6-arylpyrimidines (1a–b), 2-hydroxy derivatives (c–d) and 2-methylmercapto derivatives (4a, b) were synthesised via the reaction of either a mixture of malononitrile and aromatic aldehyde or arylidene malononitrile with thiourea, urea and S-methylisothiourea, respectively. 1c, d could also be obtained by the action of hydrogen peroxide on 1a, b or by the action of hydrochloric acid on 4a, b. Compounds 4a, b could also be prepared by the action of methyl iodide on 1a, b. 4a reacted with hydrazine hydrate to give the 2-hydrazino derivative 5 which condensed easily with aromatic aldehydes to give the Schiff’s bases 6a, b. Compound 5 could be converted into the tetrazolo- and s-triazolopyrimidines 7 and 9 by the action of nitrous acid and carbon disulphide respectively. Structures of the newly synthesised compounds were established by chemical routes and spectral studies.

In continuation to our previous work [1, 2] directed to synthesise biologically active compounds, we report here a new synthesis for 2-hydroxy-, 2-mercapto- and 2-alkylmercaptopyrimidine derivatives via the reaction of aromatic aldehydes, malononitrile and each of urea, thiourea and S-methylisothiourea respectively. The reaction products were utilised for the synthesis of other azolopyrimidines bearing latent functional substituents. Thus, when a ternary mixture of the appropriate aromatic aldehyde, malononitrile and thiourea or urea was refluxed in ethanol in the presence of potassium carbonate, the 2-mercaptopyrimidine derivatives (la–d) were obtained. The reaction proceeds probably via the formation of the non-isolable intermediates 3, which then undergo autoxidation to the final isolable 1a–d.

Structure 1 was inferred from the following facts: (a) The mercaptopyrimidine derivatives 1a, b could easily be converted into the oxygen counter analogues 1c, d by simple treatment with hydrogen peroxide, (b) The 1H NMR (δ ppm) spectrum of 1a showed signals at 3.20 (s, 1H, -SH), 7.50 (m, 2H, H arom.), 7.85 (m, 2H, H arom.) and at 8.15 (m, 2H, NH2) and addition of D2O led to the disappearance of the first and the last signals, (c) The IR spectra of 1a–d displayed characteristic bands for NH2, CN and SH (1a, b) or OH (1c, d) (cf. Experimental Part) and (d) Compounds 1a–d could also be synthesised via the reaction of the corresponding arylidene malononitrile (2a, b) with thiourea or urea in boiling pyridine (cf. Scheme 1).

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0340–5087/83/1200–1686/$ 01.00/0

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In continuation to this work, the 2-methylmercaptopyrimidine derivatives 4\textsubscript{a,b} were synthesised via the reaction of S-methylisothiourea with a mixture of malononitrile and aromatic aldehydes in ethanol. The same products (4\textsubscript{a,b}) were also obtained when the arylidene malononitriles (2\textsubscript{a,b}) were treated with S-methylisothiourea in pyridine. The reaction proceeds similar to that described in Scheme 1. Spectral data of the reaction products supports the proposed structure 4 (cf. Experimental Part). Moreover, compounds 4\textsubscript{a,b} were obtained by the action of methyl iodide on 1\textsubscript{a,b} respectively. Compounds 4\textsubscript{a,b} were readily hydrolysed by ethanolic hydrochloric acid to afford the oxygen analoges 1\textsubscript{c,d}, respectively.

When 4\textsubscript{a} was refluxed with hydrazine hydrate in ethanol till evolution of methanethiol ceased, the hydrazino derivative 5 was obtained in good yield. The latter compound (5) gave, smoothly, the Schiff’s bases 6\textsubscript{a,b} when treated with aromatic aldehydes.

Treatment of 5 with each of nitrous acid and carbon disulphide yielded, most probably, 5-phenyl-6-cyano-4-amino-tetrazolo[1,5-a]pyrimidine (7) and s-triazolo[4,3-a]pyrimidine (9) rather than their isomeric compounds 8 and 10 respectively. It appeared that structures 7 and 9 might be elucidated by physical methods rather than chemical ones. It can be seen that the phenyl group in each of 8 and 10 must be twisted out-of-plane of the pyrimidine ring because of steric interference. This phenyl group would be expected to give compact signal in \textsuperscript{1}H NMR spectrum. However, the phenyl group in each of 7 and 9 should be coplaner with the pyrimidine ring, and in agreement there is a complex two-proton signal at low field. Since the \textsuperscript{1}H NMR data of the two reaction products show that, the ortho-phenyl protons are deshielded by about 0.3 ppm relative to the meta- and para-protons (cf. Experimental Part) similar to the non-substituted N-4 products 1 and 4, this indicates that structures 7 and 9 are the exact ones for the reaction products. This is in agreement with the reported \textsuperscript{1}H NMR data for other compounds of similar systems [3, 4].

Experimental

All melting points are uncorrected. IR spectra were recorded on a Pye Unicam SP-1100 spectrophotometer. \textsuperscript{1}H NMR spectra were measured in DMSO-d\textsubscript{6} on a Varian EM-360 60 MHz spectrometer, using TMS as internal standard and chemical...
shifts δ (ppm). Elementary analyses were performed by the Microanalytical Centre, Cairo, University.

2-Mercapto- and 2-hydroxy-4-amino-5-cyano-6-arylpyrimidines (1a–d)

Method A: A mixture of the aromatic aldehyde (0.01 mole), malononitrile (0.01 mole) and thiourea (or urea) (0.01 mole) in ethanol (20 ml) containing potassium carbonate (0.01 mole) was heated under reflux for 5 h. The potassium salt of 1 which precipitated during the reaction was collected and washed with ethanol. The crude salt was stirred in warm water and filtered. The filtrate, after cooling, was acidified with acetic acid. The deposited precipitate, thus formed, was collected and washed well with water and dried in air. Recrystallisation from the proper solvent gave 1a–d (Tables I and II).

1H NMR of 1a: 3.20 (s, 1H, -SH; lost after D2O exchange), 7.50 (m, 3H, H arom), 7.85 (m, 2H, H arom), 7.50 (m, 3H, H arom), 7.45 (m, 1H, H arom), 6.25 (s, 2H, NH2).

Table I. Characterisation data of 1a–d, 4a, b, 5, 6a, b, 7 and 9.

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p [°C]</th>
<th>Solvent of yield [%] (method)</th>
<th>Formula</th>
<th>Analysis [%]</th>
<th>Carbon</th>
<th>Hydrogen</th>
<th>Nitrogen</th>
<th>Sulphur</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>267</td>
<td>Dioxane/H2O 56(A), 62(B)</td>
<td>C12H14N4S</td>
<td>57.89 57.7</td>
<td>3.53 3.6</td>
<td>24.55 24.7</td>
<td>14.05 14.2</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>304</td>
<td>DMF 52(A), 60(B)</td>
<td>C12H10O4N4S</td>
<td>55.81 55.6</td>
<td>3.90 3.7</td>
<td>21.70 21.6</td>
<td>12.40 12.3</td>
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<tr>
<td>1c</td>
<td>305</td>
<td>H2O 50(A), 60(B)</td>
<td>C12H10O4N4</td>
<td>62.25 62.3</td>
<td>3.80 3.7</td>
<td>26.40 26.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1d &gt;310</td>
<td>Acetic acid 55(A), 65(B)</td>
<td>C12H10O2N4</td>
<td>59.50 59.4</td>
<td>4.16 4.2</td>
<td>23.13 23.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>193</td>
<td>Ethanol 60(A), 65(B), 80(C)</td>
<td>C12H10N4S</td>
<td>59.50 59.6</td>
<td>4.16 4.3</td>
<td>23.13 23.0</td>
<td>13.22 13.1</td>
<td></td>
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<tr>
<td>4b</td>
<td>207</td>
<td>Ethanol 62(A), 68(B), 82(C)</td>
<td>C12H10O2N6</td>
<td>57.35 57.5</td>
<td>4.44 4.2</td>
<td>20.58 20.7</td>
<td>11.76 11.8</td>
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<tr>
<td>5</td>
<td>215</td>
<td>Ethanol 80</td>
<td>C12H10N6</td>
<td>58.39 58.3</td>
<td>4.46 4.5</td>
<td>37.15 37.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6a*</td>
<td>230</td>
<td>Acetic acid 85</td>
<td>C12H18O2N6</td>
<td>64.16 64.0</td>
<td>4.85 4.7</td>
<td>22.45 22.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6b*</td>
<td>263</td>
<td>Acetic acid 80</td>
<td>C12H20O2N6</td>
<td>62.36 62.4</td>
<td>4.98 5.0</td>
<td>20.78 20.6</td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td>233</td>
<td>Dioxane 70</td>
<td>C12H7N7</td>
<td>55.69 55.6</td>
<td>2.97 3.0</td>
<td>41.34 41.3</td>
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<td></td>
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<tr>
<td>9</td>
<td>263</td>
<td>Dioxane/H2O 72</td>
<td>C12H5N6S</td>
<td>53.73 53.6</td>
<td>3.01 2.9</td>
<td>31.93 31.4</td>
<td>11.94 12.0</td>
<td></td>
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</tbody>
</table>

* Compound crystallised with one molecule acetic acid of crystallisation.

Method B: Applying the same procedure described in method A for the preparation of 1a, b, using S-methylisothioura sulphate instead of thiourea afforded directly solid reaction products after cooling. Crystallisation from the proper solvent gave 4a, b (Tables I and II).

Method C: Methylation of 1a, b: A solution of 20 mmoles of each of 1a, b in ethanol (30 ml) was treated with methyl iodide (20 mmoles) and potassium carbonate solution (20 mmoles in 10 ml water) and then heated under reflux for 2 h. After cooling, colourless crystals were separated and recrystallised from the proper solvent to give 4a, b (m.p. and m.m.p. determinations).

Hydrolysis of 4a, b

1 g of each of 4a, b was refluxed with 50 ml ethanol and 20 ml conc. hydrochloric acid till the odour of methane thiol ceased (about 3 h). On cooling, colourless crystals were separated, collected and recrystallised from the proper solvent and
proved to be 1c, d respectively (m.p. and m.m.p.
determinations).

2-Hydrazino-4-amino-5-cyano-
6-phenylpyrimidine (5)

A solution of 4a (0.1 mole) in ethanol (50 ml) was
treated with an excess of hydrazine hydrate
(0.12 mole). The reaction mixture was refluxed for
2 h. The hydrazino derivative 5 which precipitated
during reflux was collected and crystallised (Tables I
and II).

Table II. IR data.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IR (KBr, cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>3375, 3325 (NH₂); 3200 (SH); 2220 (CN) and 1635 (C=N)</td>
</tr>
<tr>
<td>1b</td>
<td>3380, 3320 (NH₂); 3200 (SH); 2220 (CN) and 1635 (C=N)</td>
</tr>
<tr>
<td>1c</td>
<td>3400 (broad, OH and NH₂); 2190 (CN) and 1640 (C=N)</td>
</tr>
<tr>
<td>1d</td>
<td>3400 (broad, OH and NH₂); 2220 (CN) and 1635 (C=N)</td>
</tr>
<tr>
<td>4a</td>
<td>3375, 3325 (NH₂); 2220 (CN) and 1635 (C=N)</td>
</tr>
<tr>
<td>4b</td>
<td>3370, 3325 (NH₂); 2220 (CN) and 1630 (C=N)</td>
</tr>
<tr>
<td>5</td>
<td>3440, 3250 (NH₂ and NH); 2220 (CN) and 1630 (C=N)</td>
</tr>
<tr>
<td>6a*</td>
<td>3425 (OH); 3280 (NH₂); 2200 (CN); 1720 (CO) and 1635 (C=N)</td>
</tr>
<tr>
<td>6b*</td>
<td>3450 (OH); 3370, 3320 (NH₂); 2220 (CN); 1725 (CO) and 1635 (C=N)</td>
</tr>
<tr>
<td>7</td>
<td>3390, 3340 (NH₂); 2200 (CN) and 1640 (C=N)</td>
</tr>
<tr>
<td>9</td>
<td>3300, 3215 (NH₂ and NH); 2215 (CN); 1625 (C=N) and 1545 (C=S)</td>
</tr>
</tbody>
</table>

* Compound crystallised with one molecule acetic acid
of crystallisation.

Action of aromatic aldehydes on 5

To a solution of 5 (1 g) in ethanol (20 ml)
equimolecular amount of the appropriate aldehyde was
added. The reaction mixture was refluxed for 2 h
and left to cool whereby colourless crystals sep-
arated. Recrystallisation from acetic acid gave 6a, b
with one mole acetic acid of crystallisation (Tables I
and II).

5-Phenyl-6-cyano-7-amino-tetrazolo[1,5-a]-
pyrimidine (7)

To a mixture of 5 (1 g) in conc. hydrochloric acid
(3 ml) and water (3 ml) at 0 °C was gradually added
with stirring, a cooled solution of sodium nitrite
(0.5 g) in water (3 ml). The reaction mixture was
left overnight and diluted with water where upon
precipitation took place. The solid, that precipitated,
was collected and crystallised from dioxane to give 7
(Tables I and II).

1H NMR: 7.65 (m, 3H, Harom), 7.92 (m, 2H,
Harom) and 8.20 (br. s, 2H, NH₂, lost after D₂O
exchange).

1-Thioxo-1,2-dihydro-5-phenyl-6-cyano-7-amino-
s-triazolo[4,3-a]pyrimidine (9)

A mixture of 5 (1 g), methanol (50 ml), potassium
hydroxide (0.3 g) and carbon disulphide (3 ml) was
refluxed for 4 h. After removal of methanol, dilute
potassium hydroxide was added and the alkaline
solution was filtered. The clear filtrate was acidified
dilute hydrochloric acid and the formed precipi-
tate was collected and crystallised from dilute
dioxane to give 9 (Tables I and II).

1H NMR: 7.48-7.70 (m, m, 7H, 5Harom and
NH₂) and 11.32 (br. s, 1H, NH). After D₂O
exchange: 7.48 (m, 3H, Harom) and 7.70 (m, 2H,
Harom).

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