A NEW APPROACH TO 5H-PYRROLO[3,2-d]PYRIMIDINES (9-DEAZAPURINES) FROM 3-AMINOPYRROLE-2-CARBOXYLATES

Lovro Selič and Branko Stanovnik

Faculty of Chemistry and Chemical Technology, Aškerčeva 5, Ljubljana, Slovenia

Abstract — 3-Amino-4-ethoxycarbonyl-1-methyl-1H-pyrrole-2-carboxylate (2) was used to prepare 9-deazapurines in a single step reaction.

Pyrrolo[3,2-d]pyrimidines (9-deazapurines) have been substantially investigated as a part of the synthesis of new C-nucleosides with potential biomedical interest, since they have been found to exhibit pronounced growth inhibitory activity to several leukemic cell lines.1-4

9-Deazapurines have been synthesized mostly from appropriate 3-nitropyrimidines.5 Pyrroles, due to the lack of successful synthetic methods have been employed less frequently.5 In this case, first an urea or thiourea derivative has been formed under mild conditions, followed by heating in the presence of a base to achieve ring closure.1

Recently, various alkyl 2-(2,2-disubstitutedethenyl)amino-3-dimethylaminopropenoates6-13 and -butenoates14 have been synthesized as versatile reagents for the preparation of numerous heterocyclic systems. In continuation of our research, we have found that alkyl 2-[2-cyano-2-substituted ethenyl]amino-3-dimethylaminopropenoates can be transformed into the corresponding 3-aminopyrrole-2-carboxylates.15

Methyl 3-amino-4-ethoxycarbonyl-1-methyl-1H-pyrrole-2-carboxylate (2) can be easily prepared from ethyl 2-cyano-3-ethoxypropenoate (1) and methyl glycinate in 35% overall yield (Scheme 1).13,15 In this note we present a further conversion of compound (2) with various isothiocyanates and isocyanates. We found that only ester group at position 2 participates in cyclization to give 9-deazapurine derivatives.

Scheme 1

\[
\text{EtOCH=CHCN} \rightarrow \text{EtOCH=CHCN} \rightarrow \text{EtOCH=CHCN}
\]

i) NH₂CH₂COOMe•HCl, NEt₃, H₂O, EtOH
ii) DMFDMA (2.4 eq)
iii) HCl, EtOH
Compound (2) was treated with the following isocyanates or isothiocyanates: methyl isothiocyanate (3a), ethyl isocyanate (3b), ethyl isothiocyanate (3c), allyl isothiocyanate (3d), benzyl isocyanate (3e), phenyl isocyanate (3f), phenyl isothiocyanate (3g) and p-tolyl isothiocyanate (3h) to give the corresponding 3-substituted 7-ethoxycarbonyl-5-methyl-2-oxo(or thioxo)-5H-pyrrolo[3,2-d]pyrimidin-4-ones (5) (Scheme 2). Pyridine was found to be a suitable solvent and in most cases the reaction was carried out as a one-step synthesis. For the reaction of 2 with 3e chloroform was used to give an urea derivative, which was without further purification cyclised into 5e in boiling pyridine. Similarly, 2 was transformed with 3b in acetonitrile to give 4b as intermediate, followed by addition of aqueous solution of potassium hydroxide to give the cyclized product (5b) (Scheme 2).

**Scheme 2**

<table>
<thead>
<tr>
<th>3-5</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
<th>g</th>
<th>h</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Me</td>
<td>Et</td>
<td>Et</td>
<td>Allyl</td>
<td>PhCH2</td>
<td>Ph</td>
<td>Ph</td>
<td>4'-MePh</td>
</tr>
<tr>
<td>X</td>
<td>S</td>
<td>O</td>
<td>S</td>
<td>S</td>
<td>O</td>
<td>O</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

Cyclisation of urea or thiourea derivatives (4) can take place either to methoxycarbonyl group at position 2 to afford either 5H-pyrrolo[3,2-d]pyrimidine derivatives (5) or to ethoxycarbonyl group at position 4 to give 6H-pyrrolo[4,3-d]pyrimidine derivatives (6). On the basis of 1H NMR spectra of cyclized product, which show ethoxycarbonyl group, one can conclude, that in the formation of pyrimidine ring methoxycarbonyl group, attached at position 2 in pyrrole ring, participates to give derivatives of 5H-pyrrolo[3,2-d]pyrimidine system.

Methylation of 5f with dimethylformamide dimethyl acetal (DMFDMA) took place at position 1. Accordingly 7-ethoxycarbonyl-1,5-dimethyl-3-phenylpyrrolo[3,2-d]pyrimidine-2,4-dione (7) was prepared (Scheme 3).
Melting points were taken on a Kofler micro hot stage. The $^1$H NMR spectra were obtained on a Bruker Avance 300 DPX spectrometer, and microanalyses for C, H, and N on a Perkin-Elmer Analyser 2400.

Methyl 3-amino-4-ethoxycarbonyl-1-methyl-1H-pyrrole-2-carboxylate (2) was prepared according to the previously described procedure.$^{15}$

**Synthesis of 9-deazapurines. General procedure.** To a suspension of methyl 3-amino-4-ethoxycarbonyl-1-methyl-1H-pyrrole-2-carboxylate (2, 1 mmol, 226 mg) in pyridine (4 mL), appropriate isocyanate or isothiocyanate (2 mmol) was added and the mixture was heated for 5 h. After that, the volatile components were evaporated in vacuo and ethanol was added for the crystallisation. Compounds were purified by recrystallisation from an appropriate solvent.

The following compounds were prepared in this manner:

7-Ethoxycarbonyl-3,5-dimethyl-2-thioxo-5H-pyrrolo[3,2-d]pyrimidin-4-one (5a): from 2 and methyl isothiocyanate (3a), yield 66%; mp 184-188°C (toluene). $^1$H NMR (DMSO-d$_6$) δ: 1.31 (t, J= 7.1 Hz, COOEt), 3.61 (s, N6-Me), 3.94 (s, N1-Me), 4.29 (q, J= 7.1 Hz, COOEt), 7.98 (s, H$_2$), 10.89 (s, NH). Anal. Calcd for C$_{12}$H$_{12}$N$_2$O$_2$S: C, 49.43; H, 4.90; N, 15.72. Found: C, 49.05; H, 4.89; N, 15.79.

7-Ethoxycarbonyl-3-ethyl-5-methyl-2-thioxo-5H-pyrrolo[3,2-d]pyrimidin-4-one (5c): from 2 and ethyl isothiocyanate (3c), yield 60%; mp 144-168°C (ethanol/toluene 1:1). $^1$H NMR (DMSO-d$_6$) δ: 1.20 (t, J= 7.1 Hz, NEt), 1.30 (t, J= 7.1 Hz, COOEt), 3.94 (s, NMe), 4.28 (q, J= 7.1 Hz, COOEt), 4.41 (q, J= 7.1 Hz, NEt), 7.98 (s, H$_2$), 10.82 (s, NH). Anal. Calcd for C$_{12}$H$_{13}$N$_3$O$_2$S: C, 51.23; H, 5.37; N, 14.94. Found: C, 51.14; H, 5.19; N, 14.85.

3-Allyl-7-ethoxycarbonyl-5-methyl-2-thioxo-5H-pyrrolo[3,2-d]pyrimidin-4-one (5d): from 2 and allyl isothiocyanate (3d), yield 50%; mp 116-118°C (ethanol). $^1$H NMR (DMSO-d$_6$) δ: 1.30 (t, J= 7.1 Hz,
COOEt), 3.93 (s, NMe), 4.29 (q, J = 7.1 Hz, COOEt), 5.01 (d, J = 5.3 Hz, CH2), 5.12 and 5.17 (dd, J = 1.5 Hz, CH2=CH-CH2), 5.90 (m, CH2=CH-CH2), 8.00 (s, H2), 10.91 (s, NH). Anal. Calcd for C13H15N3O3S: C, 53.23; H, 5.15; N, 14.32. Found: C, 53.13; H, 5.17; N, 14.24.

7-Ethoxycarbonyl-3-phenyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-2,4-dione (5f): from 2 and phenyl isocyanate (3f), yield 85%, mp 218-221°C (methanol). 1H NMR (DMSO-d6) δ: 1.21 (t, J = 7.1 Hz, COOEt), 3.89 (s, NMe), 4.27 (q, J = 7.1 Hz, COOEt), 7.25 and 7.38-7.50 (m, Ph), 7.89 (s, H2), 10.47 (s, NH). Anal. Calcd for C16H15N3O3S: C, 61.34; H, 4.83; N, 13.41. Found: C, 61.17; H, 4.82; N, 13.56.

7-Ethoxycarbonyl-3-phenyl-5-methyl-2-thioxo-5H-pyrrolo[3,2-d]pyrimidin-5-one (5g): from 2 and phenyl isothiocyanate (3g), yield 85%; mp 215-230°C (toluene). 1H NMR (DMSO-d6) δ: 1.32 (t, J = 7.1 Hz, COOEt), 3.91 (s, NMe), 4.31 (q, J = 7.1 Hz, COOEt), 7.10-7.50 (m, Ph), 8.02 (s, H2), 11.02 (s, NH). Anal. Calcd for C16H15N3O3S: C, 58.35; H, 4.59; N, 12.76. Found: C, 58.45; H, 4.61; N, 12.62.

7-Ethoxycarbonyl-5-methyl-3-(4'-methylphenyl)-2-thioxo-5H-pyrrolo[3,2-d]pyrimidin-4-one (5h): from 2 and p-tolyl isothiocyanate (3h), yield 51%; mp 247-266°C (toluene/ethanol 1:1). 1H NMR (DMSO-d6) δ: 1.31 (t, J = 7.1 Hz, COOEt), 2.36 (s, 4'Me), 3.90 (NMe), 4.31 (q, J = 7.1 Hz, COOEt), 7.08 (d, J = 7.9 Hz, H1', H3'), 7.27 (d, J = 7.9 Hz, H2', H6'), 8.02 (s, H2), 10.97 (s, NH). Anal. Calcd for C17H17N3O3S: C, 59.46; H, 4.99; N, 12.24. Found: C, 59.12; H, 5.09; N, 12.18.

The following compounds were prepared according to different procedures:

7-Ethoxycarbonyl-3-ethyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-2,4-dione (5b): To the suspension of the compound (2) (233 mg, 1.03 mmol) in acetonitrile (3 mL), ethyl isocyanate (3b, 0.16 mL, 2 mmol) was added and the mixture was refluxed for 5 min. After that, the solution of potassium hydroxide (100 mg, 2.5 mmol) in water (1 mL) was added to the suspension and the mixture was refluxed for 55 min. The mixture was cooled and precipitate collected by filtration and recrystallized from a mixture of toluene and methanol (1:1) to give 5b (158 mg, 58%), mp 185-189°C. 1H NMR (DMSO-d6) δ: 1.10 (t, J = 7.2 Hz, NEt), 1.27 (t, J = 7.2 Hz, COOEt), 3.86-3.90 (q, J = 7.2 Hz, NEt), 3.90 (s, NMe), 4.24 (q, J = 7.2 Hz, COOEt), 7.77 (s, H2), 10.20 (s, NH). Anal. Calcd for C12H15N3O4: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.02; H, 5.89; N, 16.12.

7-Ethoxycarbonyl-3-benzyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-2,4-dione (5e): To the suspension
of the compound (2) (210 mg, 0.93 mmol) in chloroform (3 mL), benzyl isocyanate (3e, 0.23 mL, 1.4 mmol) was added and the mixture was refluxed for 5 min. After the addition of ethanol (1 mL), the precipitate was collected by filtration and refluxed in pyridine (4 mL) for 4 h. The precipitate was collected by filtration and recrystallized from mixture of toluene and ethanol (1:1) to give 5e (222 mg, 73%), mp 204-209°C. \( ^1H \) NMR (DMSO-\(d_6\)) \(\delta\): 1.28 (t, \(J=7.1\) Hz, COOEt), 3.91 (s, NMe), 4.27 (q, \(J=7.1\) Hz, COOEt), 5.03 (s, CH\(_2\)Ph), 7.23 -7.30 (m, Ph), 7.86 (s, H\(_2\)), 10.45 (s, NH). Anal. Calcd for C\(_{17}\)H\(_{17}\)N\(_3\)O\(_4\): C, 62.38; H, 5.23; N, 12.84. Found: C, 62.36; H, 5.24; N, 13.15.

**Methylation at position 1. Synthesis of 7-ethoxycarbonyl-3-phenyl-1,5-dimethyl-5H-pyrrolo[3,2-\(d\)]pyrimidine-2,4-dione (7):** To the suspension of 5f (113 mg, 0.36 mmol) in mixture of toluene (2 mL) and acetonitrile (2 mL), DMFDMAC (0.11 mL, 0.73 mmol) was added and the mixture was refluxed for 2 h. After cooling, the precipitate was collected by filtration to give 7 (80 mg, 68%), mp 266-269°C. \( ^1H \) NMR (DMSO-\(d_6\)) \(\delta\): 1.30 (t, \(J=7.1\) Hz, COOEt), 3.67 (s, N4-Me), 3.91 (s, N1-Me), 4.24 (q, \(J=7.1\) Hz, COOEt), 7.25 and 7.38-7.50 (m, Ph), 7.96 (s, H\(_2\)). Anal. Calcd for C\(_{17}\)H\(_{17}\)N\(_3\)O\(_4\): C, 62.38; H, 5.23; N, 12.84. Found: C, 62.36; H, 5.47; N, 12.94.

**ACKNOWLEDGEMENT**

The authors wish to express their gratitude to the Ministry of Science and Technology, Slovenia, for their financial support.

**REFERENCES AND NOTES**


Received, 21st December, 1998