Phosphorus Pentoxide in Organic Synthesis. XXXV.*
Synthesis of Thiazolo[5,4-d]pyrimidin-7-amines and Purine-6-thiones from 5-Acylamino-4-thiazolecarboxamides

Knud Erik Andersen, Mahmoud Hammad, Khalid M. H. Hilmy and Erik B. Pedersen

Department of Chemistry, Odense University, DK-5230 Odense M, Denmark


5-Acylamino-4-thiazolecarboxamides (1) have been converted into a series of N-aryl-7-thiazolo[5,4-d]pyrimidinamines (3) and 9-aryl-1,9-dihydro-6H-purine-6-thiones (4) by heating in a mixture of phosphorus pentoxide, triethylamine hydrochloride and an aniline. The relative proportions of 3 and 4 depend both on the structure of the arylamine and thiazole used and on the reaction temperature. The influence of these factors and a possible reaction mechanism are discussed.

Continuing our interest in the synthesis of N-aryl-7-thiazolo[5,4-d]pyrimidinamines and 9-aryl-1,9-dihydro-6H-purine-6-thiones, we now report the synthesis of a new series of such biologically interesting compounds. Compounds of this type have hitherto usually been prepared from pyridine derivatives.

In the previous paper in this series we described the reaction of readily available 5-acylamino-2-methyl-4-thiazolecarboxamides [1, R² = CH₃] with mixtures of phosphorus pentoxides and amines to give 2-methyl-7-thiazolo[5,4-d]pyrimidinamines (3). In many cases 1,9-dihydro-2-methyl-6H-purine-6-thiones (4) were isolated as by-products. The latter compounds were believed to be formed in a rearrangement reaction of 3 assuming a ring-opening reaction of the thiazole ring. The substituent R² is therefore considered to be crucial for the progress of the rearrangement. In order to confirm this we have now treated 5-acylamino-4-thiazolecarboxamide (1, R² = H) with the phosphorus pentoxide reaction mixture as follows (Scheme 1): 1 was treated with a mixture of phosphorus pentoxide, triethylamine hydrochloride and an appropriate substituted aniline at 200°C for 2

Scheme 1.

*Part 34, see Ref. 1.
Table 1. Reaction conditions and yields of 3 and 4 (R² = H).

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R²</th>
<th>R</th>
<th>React. conditions</th>
<th>Compound 3</th>
<th>Compound 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time/min Temp./°C</td>
<td>Yield/%</td>
<td>M.p. °C</td>
</tr>
<tr>
<td>a</td>
<td>CH₃</td>
<td>C₆H₅</td>
<td>60 200</td>
<td>44</td>
<td>78–80</td>
</tr>
<tr>
<td>b</td>
<td>CH₃</td>
<td>4-ClC₆H₄</td>
<td>60 240</td>
<td>29</td>
<td>181–183</td>
</tr>
<tr>
<td>c</td>
<td>CH₃</td>
<td>4-FC₆H₄</td>
<td>70 200</td>
<td>65</td>
<td>117–118</td>
</tr>
<tr>
<td>d</td>
<td>CH₃</td>
<td>4-CH₂C₆H₄</td>
<td>70 200</td>
<td>37</td>
<td>181–183</td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>3,5-(CH₃)₂C₆H₃</td>
<td>70 240</td>
<td>90</td>
<td>&gt;330</td>
</tr>
<tr>
<td>f</td>
<td>H</td>
<td>C₆H₅</td>
<td>90 240</td>
<td>51</td>
<td>&gt;335°c</td>
</tr>
<tr>
<td>g</td>
<td>H</td>
<td>4-ClC₆H₄</td>
<td>90 240</td>
<td>100</td>
<td>&gt;320</td>
</tr>
<tr>
<td>h</td>
<td>H</td>
<td>4-CH₂C₆H₄</td>
<td>80 240</td>
<td>37</td>
<td>&gt;320</td>
</tr>
<tr>
<td>i</td>
<td>H</td>
<td>3-CF₃C₆H₄</td>
<td>90 240</td>
<td>37</td>
<td>&gt;320</td>
</tr>
</tbody>
</table>

*3a,c were recrystallized from diethyl ether, and 3b,d from benzene. *4a–e,l were recrystallized from ethanol/DMF, and 4f–h,j from DMF. Lit. m.p. > 300° C.

min; the reaction was complete after 60–70 min at 160° C, giving a mixture of 3 and 4. When 5-acetyl- or 5-formylamino-4-thiazolecarboxamide were allowed to react in the same mixture at 240° C for 2 min and then at 160° C for 60–90 min, the thione 4 was obtained in good yield as the only product (Table 1).

We previously reported the isolation of 5-acetylamino-6-anilino-2-methyl-4(1H)-pyrimidinethione (5, R¹ = R² = CH₃) in a modified work-up experiment. In this work, we have also tried to isolate this type of intermediate by reaction of 5-acetylamino-4-thiazolecarboxamide, but with p-toluidine only the thione 4d was obtained.

A possible pathway for the formation of 3 is outlined in Scheme 1 (R² = H). The reaction can proceed via compound 2 by dehydration with phosphorus pentoxide. The reagent mixture is presumed to phosphorylate the oxygen atom in 2. The arylamine present in the mixture reacts with the intermediate to give 3, which via ring opening of the thiazole ring can be transformed into the corresponding isomeric 6-purinethione. When 1,9-dihydro-9-phenyl-6H-purine-6-one was treated with phosphorus pentasulfide in pyridine we obtained 1,9-dihydro-9-phenyl-6H-purine-6-thione, which has the same UV, IR, MS, ¹H NMR and ¹³C NMR spectral features as compound 4f. Another indication of the formation of 4 is the fact that in the ¹H NMR spectrum, the aromatic proton resonances of 4 appear as singlets or as multiplets, depending on the presence or absence of 8-substitution. Due to the steric hindrance in the 8-substituted 6-purinethiones a lower degree of annular conjugation is obtained, which results in a downfield shift of the C-2' signals relative to those for the 8-unsubstituted compounds.

In order to demonstrate that 2 is a likely intermediate, we heated 1 (R¹ = R² = H) without solvent at 300° C for 10 min and obtained 2 in 73% yield. Formation of 2 from 1 at 300° C explains why the better yields of 4 were obtained when the reaction mixture was heated briefly at 240° C. 2 was treated, under the same reaction conditions as 1, with the phosphorus pentoxide reagent prepared from aniline; 4f was obtained, confirming 2 as an intermediate.

The ratio of 3 to 4 formed at 240° C is significantly influenced the nature of by R². With R² = CH₃, the main products are the 7-thiazolo[5,4-d]pyrimidinamines (3), while R² = H results in the formation of 6-purinethiones (4) (Table 1). The formation of 4 is presumably initiated by attack of a nucleophile on the thiazole ring of 3 to give the amide derivative of 5. This attack is more sterically and electronically hindered for R² = CH₃ than for R² = H. When the amide is formed it presumably recyclizes at the high reaction temperature to give 4. For steric reasons, the reaction would again be favoured by R² = H compared to R² = CH₃.
The influence of \( R^1 \) on the product ratio is less markedly than that of \( R^2 \). However, the total yield is often increased when \( R^1 = H \), which can be explained by the path in Scheme 1 where \( R^1 = H \) promotes the formation of 2. Under the vigorous reaction conditions used the starting material 1 is assumed to be less stable than the products 3 and 4, and less material will therefore be destroyed for fast conversion of 1 to products.

For assignment of the \( ^{13}C \) NMR signals, coupled and decoupled measurements were used together with data for similar compounds.\(^{1,10}\) The assignments of the proton resonances from 2-H and 8-H in 4 are based on results for similar compounds obtained by NOE measurements.\(^{11}\) \( ^1H \) NMR, \( ^{13}C \) NMR, MS, UV and IR spectra were all in agreement with those expected for the compounds 3 and 4.

**Biological activities**

Compound 3b showed anthelmintic activity, and 4d and 4j were active against *Monochoria*.\(^{12}\)

**Experimental**

N-Aryl-5-methyl-7-thiazolo[5,4-d]pyrimidinamines (3a-d) and 9-aryl-1,9-dihydro-2-methyl-6H-purine-6-thiones (4a-d). \( \text{P}_{2}\text{O}_{10} \) (14.2 g, 0.05 mol), triethylamine hydrochloride (13.7 g, 0.10 mol) and freshly distilled or recrystallized arylamine (0.10 mol) are mixed at room temperature. The mixture is then heated on an oil bath at 240°C with mechanical stirring and protection by a drying tube until a clear homogeneous mixture is obtained (approx. 0.5 h). The mixture is cooled to 200°C, and 5-acetylamino-4-thiazolcarboxamide\(^{13}\) (4.63 g, 0.025 mol) is added and the mixture is stirred at 200°C for 2 min. The mixture is then cooled to 160°C and stirred for 60–70 min (Table 1) at that temperature. It is then allowed to cool to 120°C and 2 M NaOH is cautiously added with stirring until pH > 10 (200 ml). The mixture is stirred for 1 h at room temperature and then cooled in an ice bath. After extraction with \( 3 \times 75 \text{ ml of CH}_2\text{Cl}_2 \), the extract is dried with MgSO\(_4\) and evaporated in vacuo to give an oil consisting of the arylamine and 3. This oil is triturated with ether and recrystallized from a suitable solvent (Table 1) to give pure 3. The strongly alkaline aqueous solution is neutralized with 4 M HCl (pH 6). The precipitate is isolated, washed with water, and dried to give crude 4. The filtrate is extracted with \( 3 \times 50 \text{ ml of CH}_2\text{Cl}_2 \), and the extract is dried with MgSO\(_4\) and evaporated in vacuo to give another crop of 4.

3a: MS [m/z (% rel. int.)]: 242 (84, M), 241 (100), 200 (10). \( ^1H \) NMR (60 MHz, DMSO-\( d_6 \)): \( \delta \; 2.58 \text{ (5-CH}_3\text{)}, \; 6.93-8.05 \text{ (Ar-H)}, \; 9.26 \text{ (2-H)}, \; 9.97 \text{ (N'-H)}. \; ^{13}C \) NMR (15 MHz, DMSO-\( d_6 \)): \( \delta \; 25.7 \text{ (5-CH}_3\text{)}, \; 121.1 \text{ (C-2')}, \; 123.0 \text{ (C-4')}, \; 128.3 \text{ (C-3')}, \; 128.8 \text{ (C-7a)}, \; 139.1 \text{ (C-1')}, \; 151.6 \text{ (C-2)}, \; 153.1 \text{ (C-7)}, \; 162.2 \text{ (C-3a)}, \; 163.3 \text{ (C-5)}. \) IR (Nujol): 1620 (s), 1580 (s) cm\(^{-1}\). UV [abs. ethanol (logs)]: 300 (4.27), 242 (3.94) nm.

4a: MS [m/z (% rel. int.)]: 242 (100, M), 241 (5), 201 (30). \( ^1H \) NMR (60 MHz, CMSO-\( d_6 \)): \( \delta \; 2.53 \text{ (2-CH}_3\text{)}, \; 7.50-7.80 \text{ (Ar-H)}, \; 8.59 \text{ (8-H)}, \; 13.90 \text{ (N'-H)}. \; ^{13}C \) NMR (15 MHz, DMSO-\( d_6 \)): \( \delta \; 21.0 \text{ (2-CH}_3\text{)}, \; 123.9 \text{ (C-2')}, \; 128.1 \text{ (C-4')}, \; 129.4 \text{ (C-3')}, \; 133.8 \text{ (C-5)}, \; 134.1 \text{ (C-1')}, \; 141.5 \text{ (C-8)}, \; 144.2 \text{ (C-4)}, \; 155.5 \text{ (C-2)}, \; 176.7 \text{ (C-6)}. \) IR (Nujol): 1580 (s), cm\(^{-1}\). UV [abs. ethanol (logs)]: 328 (4.37), 226 (4.25) nm.

9-Aryl-1, 9-dihydro-6H-purine-6-thiones (4a, b, e–j). The mixture of phosphorus pentoxide, triethylamine hydrochloride and arylamine is prepared as above. The temperature is kept at 240°C, and \( ^1\text{H} \) \( ^{13}\text{C} \) (0.025 mol) is added and the mixture is stirred at 240°C for 2 min. The mixture is then cooled to 160°C and stirred for 60–90 min at that temperature. It is then cooled to 120°C and 200 ml of 2 M NaOH (pH > 10) is cautiously added with stirring. The stirring is continued for 1 h at room temperature. The mixture is then extracted with \( 3 \times 75 \text{ ml of CH}_2\text{Cl}_2 \), and the extract is dried with MgSO\(_4\) and evaporated in vacuo to give an oil. The oil contains no 3 according to \( ^1\text{H} \) NMR. The strongly alkaline aqueous solution is neutralized with 4 M HCl (pH 6). The precipitate is isolated, washed with water, and dried to give crude 4 (Table 1).

1,9-Dihydro-9-phenyl-6H-purine-6-thione (4f) from 1,9-dihydro-9-phenyl-6H-purin-6-one. \( \text{P}_{2}\text{S}_{5} \) (0.8 g, 0.0036 mol) is added to 20 ml of anhydrous pyridine at 65–70°C. 1,9-Dihydro-9-phenyl-6H-purin-6-one (0.53 g, 0.0025 mol) is added and the mixture is heated under reflux for 3 h with stirring. The excess of pyridine is removed in vacuo, giving a solid which is
treated with 25 ml of hot H₂O and boiled for 1 h. The precipitate is isolated, washed with water, and dried to give 4f (0.53 g, 93%). For purification, the solid is dissolved in 15 ml of 2 M NaOH, treated with activated charcoal, and filtered. The filtrate is neutralized with 4 M HCl (pH 7) to give a solid which is isolated, washed with water, and recrystallized from EtOH/DMF. The material obtained by this method has the same UV, MS, IR, ¹H NMR and ¹³C NMR spectroscopic features as 4f obtained above. MS [m/z (% rel. int.): 228 (100, M), 227 (11), 201 (16). ¹H NMR (60 MHz, DMSO-d₆): δ 7.67 (Ar-H), 8.50 (2-H), 9.29 (8-H). ¹³C NMR (15 MHz, DMSO-d₆): δ 123.9 (C-2'), 128.2 (C-4'), 129.4 (C-3'), 134.0 (C-1'). 135.6 (C-5), 142.0 (C-8), 143.4 (C-4), 145.4 (C-2), 176.1 (C-6). IR (Nujol): 1590 (s) cm⁻¹. UV [abs. ethanol (logε)]: 311 (4.20), 229 (4.17) nm.

Preparation of 1,9-dihydro-9-phenyl-6H-purine (4f) via thiazolo[5,4-d]pyrimidin-7(4H)-one. 1 (R¹ = R² = H) was heated without solvent in a test tube in an oil bath at 300°C for 10 min, and thiazolo[5,4-d]pyrimidin-7(4H)-one was isolated in 73% yield, m.p. > 360°C. MS [m/z (%): 153 (100, M⁺). UV (0.1 M HCl): 252, 258, 277 nm; lit.² UV (0.1 M HCl): 252, 258, 276 nm. Thiazolo[5,4-d]pyrimidin-7(4H)-one was treated, under the same reaction conditions as 1 in the synthesis of 4a,b,e-j, with the phosphorus pentoxide reagent prepared from aniline and triethylamine hydrochloride, and the products were worked up in the same way. A ¹³C NMR spectrum of the crude product in CF₃COOH was recorded, and the spectrum was identical with that for 4f.

References

Received May 25, 1987.