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

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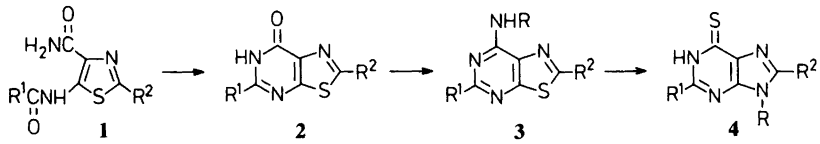
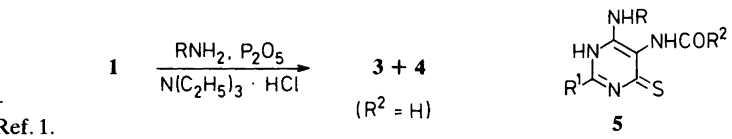
5-Acylamino-4-thiazolecarboxamides (**1**) have been converted into a series of *N*-aryl-7-thiazolo[5,4-*d*]pyrimidinamines (**3**) and 9-aryl-1,9-dihydro-6*H*-purine-6-thiones (**4**) by heating in a mixture of phosphorus pentoxide, triethylamine hydrochloride and an aniline. The relative proportions 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[2] in the synthesis of *N*-aryl-7-thiazolo[5,4-*d*]pyrimidinamines and 9-aryl-1,9-dihydro-6*H*-purine-6-thiones, we now report the synthesis of a new series of such biologically interesting[3,4] compounds. Compounds of this type have hitherto usually been prepared from pyridine derivatives.[5,6,7]

In the previous paper in this series[2] we described the reaction of readily available 5-acylamino-2-methyl-4-thiazolecarboxamides [**1**, $R^2 = CH_3$)] with mixtures of phosphorus pentoxides and arylamines to give 2-methyl-7-thiazolo[5,4-*d*]pyrimidinamines (**3**). In many cases 1,9-dihydro-2-methyl-6*H*-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 R^2 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**, R^2 = 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** (R^2 = H).

Compd.	R^1	R	React. conditions		Compound **3**		Compound **4**	
			Time/min	Temp./°C	Yield/%	M.p.[a]/°C	Yield/%	M.p.[b]/°C
a	CH_3	C_6H_5	60	200	44	78–80	21	>330
			60	240			59	
b	CH_3	4-ClC_6H_4	60	200	29	181–183	60	>330
			70	240			69	
c	CH_3	4-FC_6H_4	70	200	65	117–118	23	330–332
d	CH_3	4-$CH_3C_6H_4$	60	200	37	181–183	26	>330
e	H	3,5-$(CH_3)_2C_6H_3$	70	240			90	>330
f	H	C_6H_5	90	240			100	>345[c]
g	H	4-ClC_6H_4	90	240			51	>335[c]
h	H	4-$CH_3C_6H_4$	90	240			100	>320
i	H	3-$CF_3C_6H_4$	80	240			37	>320
j	H	3,5-$(CH_3)_2C_6H_3$	90	240			90	>330

[a] **3a,c** were recrystallized from diethyl ether, and **3b,d** from benzene. [b] **4a–e,i** were recrystallized from ethanol/DMF, and **4f–h,j** from DMF. [c] Lit.[5] 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[2] the isolation of 5-acetylamino-6-anilino-2-methyl-4(1*H*)-pyrimidinethione (**5**, R^1 = R^2 = CH_3) in a modified work-up experiment. In this work, we have also tried to isolate this type of intermediate by reaction of 5-acetylamine-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 (R^2 = 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-6*H*-purine-6-one was treated with phosphorus pentasulfide in pyridine we obtained 1,9-dihydro-9-phenyl-6*H*-purine-6-thione, which has the same UV, IR, MS, ^{1}H NMR and ^{13}C NMR spectral features as compound **4f**. Another indication of the formation of **4** is the fact that in the ^{1}H NMR spectrum, the aromatic proton resonances of **4** appear as singlets[2] or as multiplets, depending on the presence or absence of 8-substitution.[8] 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.[8]

In order to demonstrate that **2** is a likely intermediate, we heated **1** (R^1 = R^2 = 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 R^2. With R^2 = CH_3 the main products are the 7-thiazolo[5,4-*d*]pyrimidinamines (**3**),[2] while R^2 = 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 amidine derivative of **5**. This attack is more sterically and electronically hindered for R^2 = CH_3 than for R^2 = H. When the amidine is formed it presumably recyclizes at the high reaction temperature to give **4**. For steric reasons, the reaction would again be favoured by R^2 = H compared to R^2 = CH_3.

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**). P_4O_{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-thiazolecarboxamide[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 3×75 ml of CH_2Cl_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 3×50 ml of CH_2Cl_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): δ 2.58 (5-CH_3), 6.93–8.05 (Ar-H), 9.26 (2-H), 9.97 (N^7-H). ^{13}C NMR (15 MHz, DMSO-d_6): δ 25.7 (5-CH_3), 121.1 (C-2′), 123.0 (C-4′), 128.3 (C-3′), 128.8 (C-7a), 139.1 (C-1′), 151.6 (C-2), 153.1 (C-7), 162.2 (C-3a), 163.3 (C-5). IR (Nujol): 1620 (s), 1580 (s) cm^{-1}. UV [abs. ethanol (log ε)]: 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): δ 2.53 (2-CH_3), 7.50–7.80 (Ar-H), 8.59 (8-H), 13.90 (N^1-H). ^{13}C NMR (15 MHz, DMSO-d_6): δ 21.0 (2-CH_3), 123.9 (C-2′), 128.1 (C-4′), 129.4 (C-3′), 133.8 (C-5), 134.1 (C-1′), 141.5 (C-8), 144.2 (C-4), 155.5 (C-2), 176.7 (C-6). IR (Nujol): 1580 (s), cm^{-1}. UV [abs. ethanol (log ε)]: 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**[13,14] (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 3×75 ml of CH_2Cl_2, and the extract is dried with $MgSO_4$ and evaporated *in vacuo* to give an oil. The oil contains no **3** according to ^1H 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.* P_2S_5 (0.8 g, 0.0036 mol) is added to 20 ml of anhydrous pyridine at 65–70 °C. 1,9-Dihydro-9-phenyl-6*H*-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 H_2O 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, ^{1}H NMR and ^{13}C NMR spectroscopic features as **4f** obtained above. MS [*m/z* (% rel. int.)]: 228 (100, M), 227 (11), 201 (16). ^{1}H NMR (60 MHz, DMSO-d_6): δ 7.67 (Ar-H), 8.50 (2-H), 9.29 (8-H). ^{13}C NMR (15 MHz, DMSO-d_6): 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-6*H*-purine* (**4f**) *via thiazolo[5,4-*d*]-pyrimidin-7(4*H*)-one.* **1** (R^1 = R^2 = 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(4*H*)-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.[9] UV (0.1 M HCl): 252, 258, 276 nm. Thiazolo[5,4-*d*]pyrimidin-7(4*H*)-one was treated, under the same reaction conditions as **1** in the synthesis of **4a**,**b**,**e**–**j**, with the phosporus pentoxide reagent prepared from aniline and triethylamine hydrochloride, and the products were worked up in the same way. A ^{13}C NMR spectrum of the crude product in CF_3COOH was recorded, and the spectrum was identical with that for **4f**.

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