Liebigs Ann. Chem. **1986**, 1255–1261

Diphosphorus Pentaoxide in Organic Synthesis, XXVII[1]

A One-Step Synthesis of Thiazolo[5,4-*d*]pyrimidin-7-amines and Purine-6-thiones from 5-(Acylamino)-2-methyl-4-thiazolecarboxamides

Knud Erik Andersen, Mahmoud Hammad[2], and *Erik B. Pedersen**

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

Received December 23, 1985

5-(Acylamino)-2-methyl-4-thiazolecarboxamides **1** have been converted into a series of *N*-arylthiazolo[5,4-*d*]pyrimidin-7-amines **2** and 9-aryl-1,9-dihydro-6*H*-purine-6-thiones **3** by heating in a mixture of diphosphorus pentaoxide, triethylamine hydrochloride, and an appropriate substituted aniline at 240°C for 2 min and then at 160°C for 1 h. The ratio of **2** and **3** depends on the aniline and thiazole used.

Diphosphorpentaoxid in der organischen Synthese, XXVII[1]. – Eine Einschritt-Synthese von Thiazolo[5,4-*d*]pyrimidin-7-aminen und Purin-6-thionen aus 5-(Acylamino)-2-methyl-4-thiazolcarboxamiden

5-(Acylamino)-2-methyl-4-thiazolcarboxamide **1** wurden in eine Reihe von *N*-Arylthiazolo-[5,4-*d*]pyrimidin-7-aminen **2** und 9-Aryl-1,9-dihydro-6*H*-purin-6-thione **3** übergeführt, indem man sie mit einer Mischung aus Diphosphorpentaoxid, Triethylamin-hydrochlorid und einem geeigneten, substituierten Anilin 2 min auf 240°C und dann 1 h auf 160°C erhitzte. Das Verhältnis von **2** zu **3** ist abhängig vom eingesetzten Anilin und Thiazol.

As a part of our efforts to develop a new method for the synthesis of *N*-substituted thiazolo[5,4-*d*]pyrimidin-7-amines **2** and 9-substituted 1,9-dihydro-6*H*-purine-6-thiones **3** of potential biological interest[3,4], we report a new efficient one-step synthesis of these compounds.

As starting material we used of 5-(acetylamino)-2-methyl-4-thiazolecarboxamide and 5-(formylamino)-2-methyl-4-thiazolecarboxamide[5,6] which undergo a cyclization reaction with different aromatic amines in the presence of diphosphorus pentaoxide. A mixture of commercial triethylamine hydrochloride (TEA · HCl)[7], diphosphorus pentaoxide, and an appropriate substituted aniline was treated with **1** at 240°C for 2 *minutes* and the reaction was completed in another 60–90 min at 160°C (Table 1).

The formation of **2** may proceed via two pathways. A direct cyclization of **1** should lead to an intermediate thiazolo[5,4-*d*]pyrimidin-7-one which undergoes condensation with the primary amine to give **2**. On the other hand, dehydration of **1** by diphosphorus pentaoxide could give the carbonitrile **4**. Reaction of this

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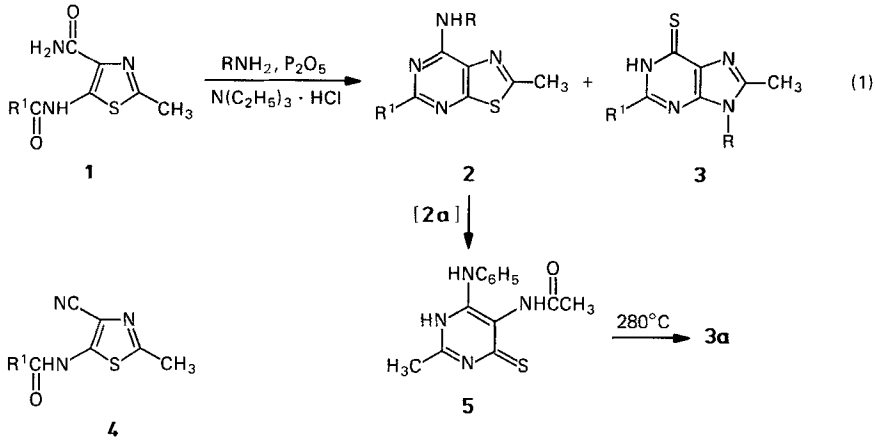
0170–2041/86/0707–1255 $ 02.50/0

Scheme 1



(1)

Table 1. Reaction of **1** according to Scheme 1, (1)

No.	R^1	R	Reaction time [min]	Compound **2** Yield [%]	Compound **2** M.p.[a] [°C]	Compound **3** Yield [%]	Compound **3** M.p.[b] [°C]
a	CH_3	C_6H_5	60	38	129–130	15	299–303
b	CH_3	4-ClC_6H_4	60	66	142–143	8	>320
c	CH_3	4-FC_6H_4	60	92	102–103	tr.	–
d	CH_3	4-$CH_3C_6H_4$	60	64	152–154	15	297–300
e	CH_3	3-$CF_3C_6H_4$	60	52	122–123	2	>330
f	CH_3	3,4-$(CH_3)_2C_6H_3$	60	44	160–163	12	205–208
g	CH_3	3,5-$(CH_3)_2C_6H_3$	85	51	181–183	10	240–242
h	CH_3	2,6-$(CH_3)_2C_6H_3$	60	6	138–140	tr.	–
i	H	C_6H_5	75	55	185–186.5[c]	25	>330
j	H	4-FC_6H_4	90	63	185–186	18	>330

[a] **2a–h** were recrystallized from petroleum ether (65–70°C), **2i** from AcOEt, and **2j** from benzene. – [b] **3a, b, d–f, i, j** were recrystallized from ethanol and **3g** from benzene. – [c] Lit.[9] m.p. 185°C.

with a primary amine to an amidine and subsequent cyclisation and rearrangement should yield **2**. As we found that **3a, 3f**, and **3g** were contaminated with a compound which afforded a nitrile (2235 cm^{-1}) and carbonyl vibration (1705 cm^{-1}) corresponding to **4**, this may be an intermediate. Further, we were able to fractionate out a compound in the mass spectra of **3e, 3f**, and **3g** which contained the following characteristic masses, *m/z* (%): 181 (M^+, 19), 139 (93), 98 (27), 59 (14), 43 (100), which are in agreement with the structure **4** (R^1 = methyl). Peak matching on *m/z* = 181 for **3f**, Calc./Found: 181.0310/181.0303.

The isolation of low to moderate yields of the compounds **3** as well as the isolation of 5-(acetylamino)-6-anilino-2-methyl-4(1*H*)-pyrimidinethione (**5**) in a modified work-up experiment – **2a** was hydrolyzed at 160°C – may give an

idea about this reaction. Compounds analogeous to **5** serve a starting materials for preparation of thiazolo[5,4-*d*]pyrimidin-7-amines and purine-6-thiones from pyrimidines[8,9,10,11]. The formation of **3** is presumably due to the attack of the nucleophilic reagents on the thiazole ring of **2** to give an amidine derivative of **5** which cyclizes at elevated temperatures.

The structures of compounds **2** and **3** were confirmed through their IR, mass, ^{1}H NMR, and ^{13}C NMR (coupled and decoupled) spectra. The data are given in Table 2–6. The two types of compounds show a distinct difference between their mass spectra. The mass spectra of the compounds **2** show a very abundant [M − 1] (**2a–g, i, j**) or [M − 15] (**2h**) peak (Table 2) which is almost absent in the mass spectrum of **3**. These intense [M − 1] and [M − 15] peaks can be explained by removal of an aromatic *ortho*-proton or *ortho*-methyl group and subsequent formation of a stabilized five-membered ring system[12]. The interpretation of the ^{13}C NMR spectra of **3** was based on data of similar compounds[13]. The deshielding effect of sulfur shifts all the resonances to lower field compared to analogeous adenines[12]. The C-2 and C-5 resonances in **2a–g** were assigned due to their quartet patterns in the coupled spectra. The C-3a resonance was difficult to observe in the spectra of **2a–g** due to its weakness and location in the stronger C-2 and C-5 resonances, but it was identified in the coupled spectra of **2i, j** by a doublet at low field due to coupling with 5-H. The C-7 resonance was assigned in **2i, j** by a doublet of doublets in the coupled spectra due to coupling with 5-H and 7-N*H*. Correspondingly, the C-7 resonance of **2a–g** was identified as a singlet in the coupled spectra at a slightly higher field due to the shielding effect of the methyl group introduced. The C-7a resonance was assumed to be at highest field due to a high electronic density at this position as for analogeous adensines[12]. The resonance appeared as a very weak singlet in the coupled spectra or it was totally absent due to overlap with the intense aromatic signals.

Biological Activities

The thiazolo[5,4-*d*]pyrimidin-7-amine **2j** was active against nematodes and showed fungicidal activity against *Phytophthora infestans* on tomato and against *Botrytis cinerea* on apple[14].

Experimental

N-Aryl-2-methylthiazolo[5,4-d]pyrimidin-7-amines (**2a–j**) *and 9-Aryl-1,9-dihydro-8-methyl-6H-purine-6-thiones* (**3a–j**): P_4O_{10} (8.5 g, 0.03 mol), triethylamine hydrochloride (8.2 g, 0.06 mol), and the substituted aniline (0.06 mol freshly distilled or recrystallized) are mixed at room temperature and then heated on an oil bath at 240 °C with mechanical stirring and protected by a drying tube until a clear homogeneous mixture is obtained (approx. 1/2 h). **1**[5,6] (0.015 mol) is added and the mixture is heated at 240 °C for 2 min. Then the mixture is allowed to cool to 160 °C and stirred for 60–90 min (Table 1) at 160 °C. When the starting material has disappeared on TLC, the mixture is allowed to cool to 120 °C. 2 M NaOH is cautiously added with stirring until pH > 10 (approx. 200 ml). The mixture is stirred for 1 h at room temperature and then cooled on an ice bath. The precipitate is isolated and washed with water to give crude **2**. The strongly alkaline filtrate and wash water are extracted with 3 × 50 ml CH_2Cl_2. The combined CH_2Cl_2 phases are dried with $MgSO_4$ and evaporated *in vacuo* to give crude **2** contaminated with the aniline (Table 1). The strongly alkaline solution from above is then neutralized with 4 M HCl (pH 6). The precipitate is isolated, washed with water, and dried to give crude **3**. The filtrate is extracted with 3 × 50 ml CH_2Cl_2. The combined extracts are dried with $MgSO_4$ and evaporated *in vacuo* to give **3**

Table 2. Spectroscopical data of compounds **2, 3,** and **5**

No.	IR (Nujol) [cm^{-1}]	MS *m/z* (%) M^+	$[M-1]^+$	Other *m/z*
2a	3400, 1610 (s), 1583 (m)	256 (83)	255 (100)	214 (6)
2b	3280, 1618 (s), 1575 (m)	290 (100)	289 (87)	292 (38), 291 (48), 249 (6)
2c	3400, 1617 (s), 1592 (s)	274 (100)	273 (95)	233 (10), 191 (12)
2d	1618 (s), 1578 (m)	270 (88)	269 (100)	229 (2), 228 (2)
2e	3400, 1620 (s), 1598 (s)	324 (100)	323 (82)	283 (14), 282 (8)
2f	3335, 1620 (m), 1610 (s)	284 (100)	283 (84)	269 (4), 243 (3), 242 (4)
2g	3320, 1618 (s), 1590 (s)	284 (100)	283 (74)	243 (5), 242 (9)
2h	3260, 1634 (s), 1607 (m)	284 (100)	283 (8)	269 (90), 243 (29), 242 (7)
2i	3325, 1615 (s), 1585 (s)	242 (69)	241 (100)	214 (2)
2j	3325, 1615 (s), 1585 (s)	260 (85)	259 (100)	232 (2), 218 (3)
3a	1595 (s), 1575 (s)	256 (100)	255 (8)	215 (36)
3b	1600, 1585 (s)	290 (100)	289 (5)	292 (38), 249 (44)
3d	1580 (s)	270 (100)	269 (8)	229 (36)
3i	1610 (s), 1590 (s)	242 (100)	241 (18)	215 (10), 214 (4)
3j	1605 (m), 1590 (s)	260 (100)	259 (14)	233 (14)
5	3295 (m), 1654 (s), 1625 (s)	274 (100)	273 (1)	232 (62), 231 (44)

Table 3. ^1H NMR[a] of thiazolo[5,4-*d*]pyrimidin-7-amines **2**

No.	2-CH_3	5-CH_3	5-H	7-NH	Ar-H	Other H
2a	2.77	2.68		—[b]	6.93–7.92	
2b	2.78	2.67		—[b]	7.21–7.86	
2c	2.78	2.67		—[b]	6.90–7.88	
2d	2.76	2.67		—[b]	7.06–7.75	2.32 (CH_3)
2e	2.80	2.70		—[b]	7.26–8.26	
2f	2.77	2.67		7.72	7.06–7.54	2.27 (CH_3), 2.30 (CH_3)
2g	2.78	2.67		7.70	7.05–7.52	2.28 (CH_3)
2i	2.87		8.46	9.7	6.92–8.00	
2j	2.87		8.48	10.0	7.04–8.07	

[a] The spectra of **2a–g** are recorded in $CDCl_3$ and **2i, j** in [D_6]DMSO. — [b] The signal is found in the aromatic multiplet.

Table 4. ^1H NMR in [D_6]DMSO of purine-6-thiones **3**

No.	2-CH_3	8-CH_3	2-H	N^1-H	Ar-H	Other H
3a	2.43	2.36		13.7	7.56	
3b	2.44	2.38		13.8	7.48–7.78	
3d	2.43	2.34		13.7	7.37	2.43 (CH_3)
3i		2.41	8.10	14.0	7.57	
3j		2.40	8.10	13.9	7.29–7.78	

Table 5. ^{13}C NMR[a] of thiazolo[5,4-*d*]pyrimidin-7-amines **2**

No.	C-2	C-3a	C-5	C-7	C-7a	2-CH_3	5-CH_3
2a	163.5[b]		163.3[b]	152.1	128.9	20.2	26.0
2b	163.5[b]	163.2[b]	163.4[b]	151.7	129.1	20.1	25.9
2c	163.5[b]		163.4[b]	151.9	129.0	20.1	26.0
2d	163.6[b]		163.1[b]	152.1	129.0	20.1	26.0
2e	163.8[b]		163.4[b]	151.7	129.1	20.1	25.8
2f	163.5[b]		162.9[b]	152.2	129.1	20.1	26.0
2g	163.6[b]		163.0[b]	152.1	129.2	20.1	26.0
2i	164.5	162.4	153.7	152.5	131.2	20.2	
2j	163.9	162.6	153.3	152.3	130.4	19.9	

No.	C-1′	C-2′	C-3′	C-4′	C-5′	C-6	Other C
2a	138.6	119.7	128.8	123.2			
2b	137.1	120.7	128.7	128.0			
2c	134.6[c]	121.4[c]	115.4[c]	158.7[c]			
2d	135.9	119.3	129.3	132.9			20.7 (CH_3)
2e	139.2	116.5[d]	131.0[d]	119.4[d]	129.3	122.3	123.8[d] (CF_3)
2f	136.9	121.1	136.2	131.6	129.8	117.4	19.0 (CH_3), 19.9 (CH_3)
2g	138.3	117.5	138.4	125.1			21.4 (CH_3)
2i	138.1	120.2	128.9	123.7			
2j	135.3[e]	123.2[e]	114.8[e]	158.1[e]			

[a] The spectra of **2a**–**i** are recorded in $CDCl_3$ and **2j** in [D_6]DMSO. – [b] The signals may be interchanged. – [c] $J_{C\text{-}1',F}$ = 2.5 Hz, $J_{C\text{-}2',F}$ = 7.8 Hz, $J_{C\text{-}3',F}$ = 22.5 Hz, $J_{C\text{-}4',F}$ = 243 Hz. – [d] $J_{C\text{-}2',F}$ = $J_{C\text{-}4',F}$ = 3.9 Hz, $J_{C\text{-}3',F}$ = 32 Hz, $J_{C\text{-}7',F}$ = 269 Hz. – [e] $J_{C\text{-}1',F}$ = 2.4 Hz, $J_{C\text{-}2',F}$ = 7.8 Hz, $J_{C\text{-}3',F}$ = 22.5 Hz, $J_{C\text{-}4',F}$ = 240 Hz.

Table 6. ^{13}C NMR in [D_6]DMSO of purine-6-thiones **3**

No.	C-2	C-4	C-5	C-6	C-8	2-CH_3	8-CH_3
3a	154.8	146.1	132.2	175.0	150.2	20.8	14.2
3b	155.0	146.1		175.1	150.1	20.8	14.2
3d	154.7	146.1	132.2	175.0	150.3	20.8	14.2
3i	144.8	145.5	134.1	174.5	150.7		14.3
3j	144.9	145.6	134.1	174.5	150.9		14.2

No.	C-1′	C-2′	C-3′	C-4′	Other C
3a	133.6	127.4	129.4	129.1	
3b	132.4	129.3[a]	129.5[a]	133.9	
3d	130.9	127.1	129.9	138.8	20.6 (CH_3)
3i	133.4	127.3	129.4	129.2	
3j	129.8	129.7[b]	116.4[b]	162.0[b]	

[a] The signals may be interchanged. – [b] $J_{C\text{-}2',F}$ = 8.8 Hz, $J_{C\text{-}3',F}$ = 23.4 Hz, $J_{C\text{-}4',F}$ = 247 Hz.

Table 7. Analysis or M^+ peak matching of compounds **2, 3,** and **5**

No.	Molecular formula (mol. weight)	Analysis or M^+ Calc. (Found) C	H	N
2a	$C_{13}H_{12}N_4S$ (256.3)	60.9 (60.9)	4.7 (4.7)	21.9 (22.2)
2b	$C_{13}H_{11}ClN_4S$ (290.8)	53.7 (54.1)	3.8 (3.8)	19.3 (19.3)
2c	$C_{13}H_{11}FN_4F$ (274.3)	56.9 (57.1)	4.0 (4.2)	20.4 (20.5)
2d	$C_{14}H_{14}N_4S$ (270.4)	62.2 (62.2)	5.2 (5.3)	20.7 (21.1)
2e	$C_{14}H_{11}F_3N_4S$ (324.3)	51.9 (52.1)	3.4 (3.6)	17.3 (17.4)
2f	$C_{15}H_{16}N_4S$ (284.4)	63.4 (63.7)	5.7 (5.7)	19.7 (20.0)
2g	$C_{15}H_{16}N_4S$ (284.4)	63.4 (63.6)	5.7 (5.7)	19.7 (19.9)
2h	$C_{15}H_{16}N_4S$	284.1096 (284.1095)		
2j	$C_{12}H_9FN_4S$ (260.3)	55.4 (55.3)	3.5 (3.6)	21.5 (21.8)
3a	$C_{13}H_{12}N_4S$ (256.3)	60.9 (60.7)	4.7 (4.8)	21.9 (21.9)
3b	$C_{13}H_{11}ClN_4S$ (290.8)	53.7 (53.5)	3.8 (3.9)	19.3 (19.5)
3d	$C_{14}H_{14}N_4S$ (270.4)	62.2 (62.2)	5.2 (5.3)	20.7 (21.1)
3e	$C_{14}H_{11}F_3N_4S$	324.0657 (324.0645)		
3f	$C_{15}H_{16}N_4S$	284.1096 (284.1100)		
3g	$C_{15}H_{16}N_4S$	284.1096 (284.1095)		
3i	$C_{12}H_{10}N_4S$ (242.3)	59.5 (59.5)	4.2 (4.3)	23.1 (23.3)
3j	$C_{12}H_9FN_4S$ (260.3)	55.4 (55.3)	3.5 (3.5)	21.5 (21.8)
5	$C_{13}H_{14}N_4OS$ (274.3)	56.9 (56.6)	5.1 (5.2)	20.4 (20.6)

which is recrystallized from a suitable solvent (Table 1) to give an analytical pure sample. In case of too little material peak matching is used instead of elemental analysis (Table 7).

5-(Acetylamino)-6-anilino-2-methyl-4(1H)-pyrimidinethione (**5**): The procedure is as described for **3a**. But instead of adding 200 ml of NaOH at 120°C, 10 ml of 2 M NaOH is added at 160°C and the stirring is continued for 5.5 h. The mixture is cooled to 120°C and 190 ml of 2 M NaOH is added. After stirring for 30 min at room temperature crude **5** (3.2 g, 83%) is isolated as a solid. The alkaline water phase is extracted with 3 × 50 ml of CH_2Cl_2 which are discarded. The alkaline water phase is neutralized with 4 M HCl (pH 6) and extracted with 3 × 50 ml of CH_2Cl_2 which are combined, dried with $MgSO_4$, and evaporated *in vacuo* to give 0.6 g (15%) of **3a**.

When **5** is heated at 280°C for 15 min compound **3a** is obtained. **5**: M.p. 291–292°C (DMF). – ^{1}H NMR ([D$_6$]DMSO/TMS): δ = 2.13 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 7.09–7.76

(m, 5H, Ar-H), 8.79 (s, 1H, NH), 8.89 (s, 1H, NH), 13.2 (br s, 1H, NH). – ^{13}C NMR ([D$_6$]DMSO/TMS): δ = 20.8 (CH_3), 23.2 (CH_3), 113.7 (C-5), 122.6 (C-2′), 123.5 (C-4′), 128.2 (C-3′), 138.6 (C-1′), 153.0 (C-6), 156.7 (C-2), 169.6 (C=O), 174.5 (C-4).

CAS Registry Numbers

1 (R′=H): 31785-14-5 / **1** (R′=Me): 5532-53-6 / **2a**: 100841-30-3 / **2b**: 100841-31-4 / **2c**: 100841-32-5 / **2d**: 100841-33-6 / **2e**: 100841-34-7 / **2f**: 100841-35-8 / **2g**: 100841-36-9 / **2h**: 100841-37-0 / **2i**: 100841-38-1 / **2j**: 100841-39-2 / **3a**: 100841-40-5 / **3b**: 100841-41-6 / **3d**: 100841-42-7 / **3e**: 100841-43-8 / **3f**: 100841-44-9 / **3g**: 100841-45-0 / **3i**: 100841-46-1 / **3j**: 100841-47-2 / **4** (R′=Me): 100841-48-3 / **5**: 100841-49-4 / TEA · HCl: 554-68-7 / $PhNH_2$: 62-53-3 / 4-$ClC_6H_4NH_2$: 106-47-8 / 4-$FC_6H_4NH_2$: 371-40-4 / 4-$CH_2C_6H_4NH_2$: 106-49-0 / 3-$CF_3C_6H_4NH_2$: 98-16-8 / 3,4-$(CH_3)_2C_6H_3NH_2$: 95-64-7 / 3,5-$(CH_3)_2C_6H_3NH_2$: 108-69-0 / 2,6-$(CH_3)_2C_6H_3NH_2$: 87-62-7 / P_2O_5: 1314-56-3

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[215/85]