Synthesis of Pyrido[2,3-*d*]pyrimidines and Fused Tetracyclic Derivatives from Methyl *N*-Aryldithiocarbamates

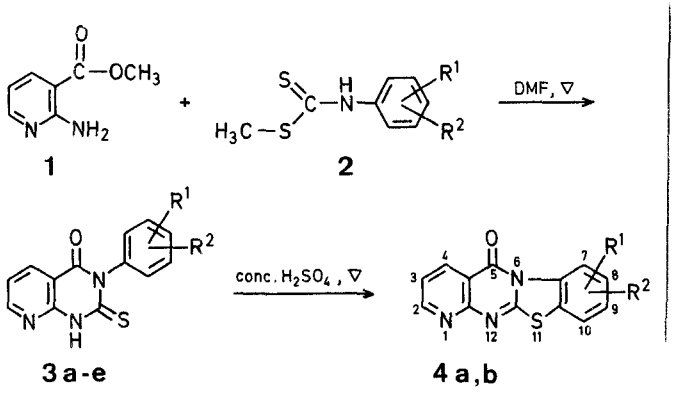
J. GARIN, E. MELENDEZ, F. L. MERCHÁN*, T. TEJERO

Departamento de Química Orgánica, Universidad de Zaragoza, Zaragoza Spain

Recently we reported[1] the synthesis of 5-oxo-5*H*-pyrido[3′,2′:5,6]pyrimido[2,1-*b*][1,3]benzothiazoles and, as a logical extension of this work, we decided to prepare their linear isomers, 5-oxo-5*H*-pyrido[2′.3′:4,5]pyrimido[2,1-*b*][1,3]benzothiazoles **4**. As 2-chloropyridine-3-carboxylic acid is known to react with aromatic amines to yield 2-arylaminopyridine-3-carboxylic acids[2], we tried its reaction with 2-aminobenzothiazoles in order to obtain the corresponding 2-(1,3-benzothiazol-2-ylamino)-pyridine-3-carboxylic acids which, upon cyclodehydration, would afford the desired products **4**. However, this procedure did not give the expected results. Under a variety of conditions (melt, reflux of xylene) only a mixture of several products could be obtained. Two of them were identified as the *N*-(1,3-benzothiazol-2-yl)-2-chloropyridine-3-carboxamide and the angular fused tetracyclic derivative[1] by comparison with authentic samples.

An alternative synthesis of the desired acids also failed, as 2-aminopyridine-3-carboxylic acid and 2-chloro-1,3-benzothiazole could not be brought to reaction. Thus, a different approach to the synthesis of compounds **4** had to be sought.

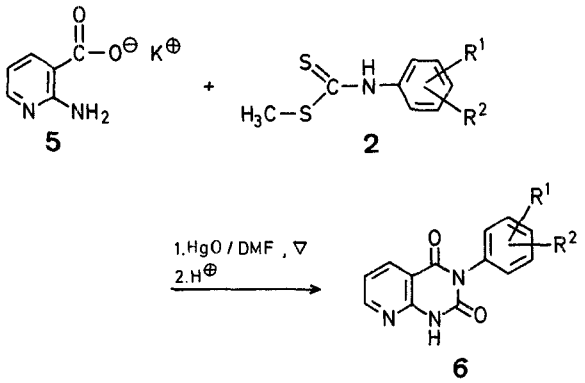
Instead of constructing the pyrimidine ring, the thiazole moiety should be easily accessible, for example, by oxidizing the appropriate thiourea, a classical synthesis of benzothiazoles[3,4]. The starting compound would be the corresponding 3-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine[5,6] **3** which, in turn, could be obtained by the reaction of 2-aminopyridine-3-carboxylic acid with methyl *N*-aryldithiocarbamates[7,8] **2**. This was the chosen synthetic route, only methyl 2-aminopyridine-3-carboxylate **(1)** was used instead of the free acid (Scheme **A**), because desulfurization took place in the reactions performed with the latter, giving rise to a mixture of the desired 2-thioxo compound and the corresponding 3-aryl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine[5,9] **6**.



Scheme **A**

Products **3** (Table 1), obtained in moderate yields using dimethylformamide as solvent, were treated with hot concentrated sulfuric acid. Compounds **3a** and **3b** underwent oxidation to give the desired fused derivatives **4** (Table 2). The presence of one methoxy group **(3c)** or two methyl groups **(3d–e)** in the aromatic ring prevented the cyclization, yielding a mixture of sulfonated, water-soluble products instead. In order to avoid this undesired reaction, dilute sulfuric acid (1 : 1) was used, but only 3-aryl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidines **6** could be obtained, probably due to acidic hydrolysis of the 2-thioxo group. A similar reaction is described for 3-aryl-2-alkylmercapto-4-oxo-3,4-dihydroquinazolines[10].

The structure of the hydrolysis products was established by an alternative synthesis (Scheme **B**) based on previous results from our laboratory[11] which makes use of the reaction of potassium 2-aminopyridine-3-carboxylate **(5)** with compounds **2** in the presence of red mercury(II) oxide in refluxing dimethylformamide (Table 3).



Scheme **B**

Melting points were determined using a Büchi 510 apparatus and are uncorrected. I.R. spectra were recorded on a Perkin-Elmer 283 instrument. ^{1}H-N.M.R. spectra were obtained on a Perkin-Elmer R-12-B spectrometer with TMS as internal reference.

3-Aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidines 3; General Procedure:

A stirred solution of methyl 2-aminopyridine-3-carboxylate (**1**; 0.304 g, 2 mmol) and the methyl *N*-aryldithiocarbamate **2** (2 mmol) in dimethylformamide (8 ml) is refluxed for 24 h, then cooled and poured into water (75 ml) to yield the crude product **3**, which is isolated by suction, washed with hexane, dried, and recrystallized (Table 1).

Table 1. 3-Aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidines **3**

Product	R^1	R^2	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a] or Lit. m.p. [°C]	I.R. (Nujol) [cm^{-1}] ν_{NH}	$\nu_{C=O}$	$\nu_{C=S}$	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]
3a	H	H	50	>300° (CH_3CN)	275–276°[6]	3060	1700	1220	8.8–8.6 (dd, 1H, 7-H); 8.5–8.3 (dd, 1H, 5-H); 7.6–7.2 (m, 6H)
3b	H	4′-CH_3	40	>300° (CH_3CN)	$C_{14}H_{11}N_3OS$ (269.3)	3070	1700	1220	8.8–8.6 (dd, 1H, 7-H); 8.4–8.2 (dd, 1H, 5-H); 7.5–7.0 (m, 5H); 2.35 (s, 3H, CH_3)
3c	H	4′-OCH_3	40	>300° (CH_3CN)	$C_{14}H_{11}N_3O_2S$ (285.3)	3060	1700	1210	8.8–8.6 (dd, 1H, 7-H); 8.4–8.2 (dd, 1H, 5-H); 7.5–6.9 (m, 5H); 3.85 (s, 3H, OCH_3)
3d	2′-CH_3	4′-CH_3	40	270–272° (CH_3CN)	$C_{15}H_{13}N_3OS$ (283.3)	3095	1705	1215	8.8–8.6 (dd, 1H, 7-H); 8.4–8.2 (dd, 1H, 5-H); 7.5–7.2 (dd, 1H, 6-H); 7.1–6.7 (m, 3H); 2.35 (s, 3H, 4′-CH_3); 2.0 (s, 3H, 2′-CH_3)
3e	3′-CH_3	5′-CH_3	35	>300° (CH_3CN)	$C_{15}H_{13}N_3OS$ (283.3)	3060	1695	1230	9.4–9.2 (dd, 1H, 7-H); 9.1–8.9 (dd, 1H, 5-H); 8.2–7.9 (dd, 1H, 6-H); 7.5–7.2 (m, 3H); 2.45 (s, 6H, $2CH_3$)[b]

[a] Satisfactory microanalyses obtained: C, ±0.16; H, ±0.17; N, ±0.19.
[b] In trifluoroacetic acid.

Table 2. 5-Oxo-5*H*-pyrido[2′,3′:4,5]pyrimido[2,1-*b*] [1,3]benzothiazoles **4**

Product	R^1	R^2	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a]	I.R. (Nujol) [cm^{-1}] $\nu_{C=O}$	^{1}H-N.M.R. (CF_3COOH) δ [ppm]
4a	H	H	36	237–238° (DMF)	$C_{13}H_7N_3OS$ (253.3)	1690	9.6–9.3 (dd, 1H, 2-H); 9.1–8.8 (m, 2H, 4-H + 7-H); 8.1–7.5 (m, 4H)
4b	H	9-CH_3	36	282–284° (DMF)	$C_{14}H_9N_3OS$ (267.3)	1690	9.6–9.4 (dd, 1H, 2-H); 9.1–8.7 (m, 2H, 4-H + 7-H); 8.1–7.8 (dd, 1H, 3-H); 7.8–7.5 (m, 2H); 2.6 (s, 3H, CH_3)

[a] Satisfactory microanalyses obtained: C, ±0.09; H, ±0.13; N, ±0.17.

Table 3. 3-Aryl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidines **6**

Product **6**	R^1	R^2	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a] or Lit. m.p. [°C]	I.R. (Nujol) [cm^{-1}] ν_{NH}	$\nu_{C=O}$	^{1}H-N.M.R. (CF_3COOH) δ [ppm]
6a	H	H	47	>300° (butanol)	–[b]	3060	1720, 1670	9.3–9.1 (dd, 1H, 7-H); 9.0–8.8 (dd, 1H, 5-H); 8.0–7.2 (m, 6H)
6b	H	4′-CH_3	46	>300° (butanol)	–[c]	3060	1720, 1670	9.4–9.2 (dd, 1H, 7-H); 9.1–8.9 (dd, 1H, 5-H); 8.0–7.7 (dd, 1H, 6-H); 7.6–7.1 (m, 4H); 2.5 (s, 3H, CH_3)
6c	H	4′-OCH_3	44	>300° (butanol)	–[c]	3060	1720, 1670	9.3–9.1 (dd, 1H, 7-H); 9.0–8.8 (dd, 1H, 5-H); 8.0–7.7 (dd, 1H, 6-H); 7.4–7.0 (m, 4H); 3.95 (s, 3H, OCH_3)
6d	2′-CH_3	4′-CH_3	40	275–276° (butanol)	$C_{15}H_{13}N_3O_2$ (267.3)	3060	1715, 1670	9.3–9.1 (dd, 1H, 7-H); 9.0–8.8 (dd, 1H, 5-H); 8.0–7.7 (dd, 1H, 6-H); 7.4–7.1 (m, 3H); 2.4 (s, 3H, 4′-CH_3); 2.15 (s, 3H, 2′-CH_3)
6e	3′-CH_3	5′-CH_3	50	>300° (butanol)	$C_{15}H_{13}N_3O_2$ (267.3)	3070	1725, 1685	9.3–9.1 (dd, 1H, 7-H); 9.0–8.8 (dd, 1H, 5-H); 8.0–7.7 (dd, 1H, 6-H); 7.3–6.9 (m, 3H); 2.35 (s, 6H, $2CH_3$)

[a] Satisfactory microanalyses obtained: C, ±0.19; H, ±0.13; N, ±0.12.
[b] Ref.[9], melting point not reported.
[c] Ref.[12], melting point not reported.

5-Oxo-5*H*-pyrido[2′,3′:4,5]pyrimido[2,1-*b*] [1,3]benzothiazoles 4; General Procedure:

A solution of the corresponding compound **3** (1 mmol) in concentrated sulfuric acid (3 ml) is heated at 130–140°C for 5 h. The mixture is cooled, poured into water (50 ml), and filtered. The filtrate is neutralized with sodium hydrogen carbonate solution and the precipitate obtained is isolated by suction and purified by recrystallization (Table 2).

3-Aryl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidines 6; General Procedure:

To a vigorously stirred suspension of potassium 2-aminopyridine-3-carboxylate **5**; (0.528 g, 3.0 mmol) and red mercury(II) oxide (0.81 g, 3.7 mmol) in dimethylformamide (15 ml), a solution of methyl *N*-aryldithiocarbamate **2** (3.0 mmol) in dimethylformamide (15 ml) is added at room temperature. The mixture is refluxed for 15 h, cooled and filtered. The solution obtained is poured into water (200 ml), ice-cooled, and acidified (pH = 6) with concentrated hydrochloric acid; the solid formed is isolated by suction, dried, and the crude product is purified by recrystallization (Table 3).

Received: November 22, 1983

[1] F.L. Merchán, J. Garin, E. Melendez, T. Tejero *Synthesis* **1983**, 154.
[2] A. Marcincal-Lefebvre et al. *Ann. Pharm. Fr.* **38**, 243 (1980); *C.A.* **94**, 15515 (1981).
[3] T.S. Griffin, T.S. Woods, D.L. Klayman *Adv. Heterocyclic Chem.* **18**, 99 (1975).
[4] J.E. McCarty, *J. Org. Chem.* **27**, 2672 (1962).
[5] A. Dornow, D. Wille, *Chem. Ber.* **98**, 1505 (1965).
[6] A.P. Bhaduri, N.M. Khanna, *Indian J. Chem.* **4**, 447 (1966).
[7] J. Garin, V. Martinez, J. Mayoral, E. Melendez, F. Merchán, *Synthesis* **1981**, 961.
[8] J. Mayoral, E. Melendez, F. Merchán, J. Sanchez, *Synthesis* **1981**, 962.
[9] M.E. Konshin, Yu.V. Kozhevnikov, A.I. Mikhalev, *U.S.S.R. Patent* 525686 (1976); *C.A.* **86**, 16700 (1977).
[10] J.E. McCarty, E.L. Haines, C.A. VanderWerf, *J. Am. Chem. Soc.* **82**, 964 (1960).
[11] J. Garin, E. Melendez, F.L. Merchán, T. Tejero, E. Villarroya, *Synthesis* **1983**, 406.
[12] A.I. Mikhalev, Yu.V. Kozhevnikov, M.E. Konshin, *Tr. Permsk. Skh. Inst.* **118**, 57 (1976); *C.A.* **86**, 121288 (1977).