Synthesis of Pyrido[2,3-*d*]pyrimidines in the Reaction of 6-Amino-2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinone with Chalcones

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Received February 3, 1992

6-Amino-2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinone (**1**) reacts in boiling DMF with α,β-unsaturated ketones **2** yielding the pyrido[2,3-*d*]pyrimidine systems **5** and **6**, respectively. The orientation in the addition process can be determined by nmr measurements, especially by NOE difference spectroscopy. The products do not correspond to a normal Skraup or Doebner-v. Miller synthesis.

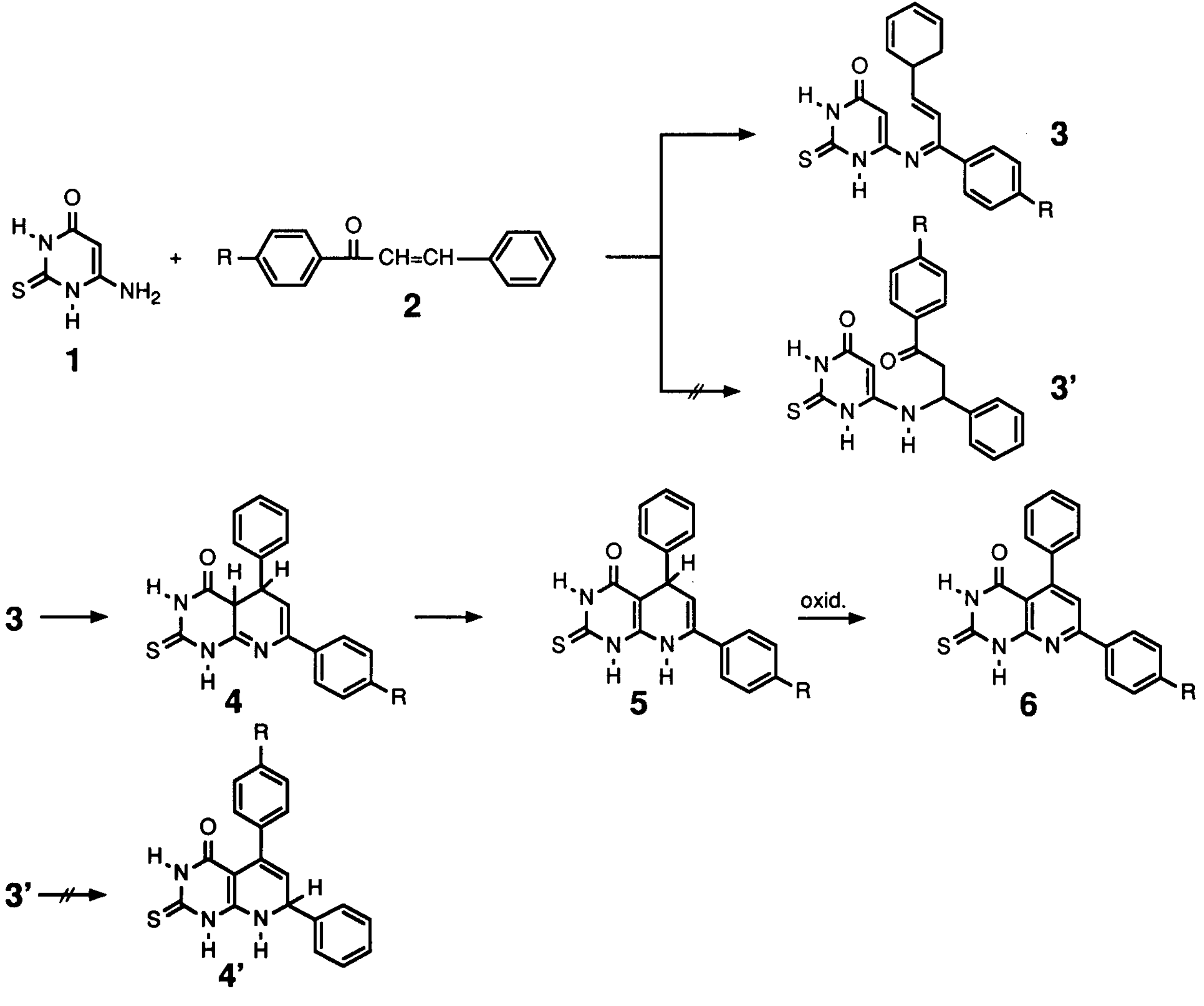
J. Heterocyclic Chem., **29**, 1045 (1992).

The pyrido[2,3-*d*]pyrimidines and their oxo and thioxo derivatives deserve great interest by virtue of their biological and physiological properties [1-15]. The reaction of heterocyclic amines and aromatic α,β-unsaturated ketones is a very convenient and versatile method for the fusion of a pyridine ring to the preexisting heterocycle [16-19]. Principally, the nucleophilic amines **1** can attack on the carbonyl carbon atom C-1 or on C-3 of the ketones **2**. The latter case would correspond to the normal Skraup and Doebner-v. Miller synthesis of pyridines and quinolines, respectively [20,21]. Nevertheless, the chemoselective formation of **3** or **3′** does not only depend on the educts but in some examples also on the reaction conditions [17,21-24]. Thus, 6-aminothiouracil (**1**), which exists at least in the solid state mainly in the thioxo-oxo-amino form [25], could enter a cyclization reaction with **2** forming the 5,7-diaryl-2,3,5,8-tetrahydro-2-thioxopyrido[2,3-*d*]pyrimidin-4(1*H*)-ones **4** or **4′**. Actually, only *one* reaction route is realized. Depending on the reaction conditions, the compounds **5** or **6** were isolated. Boiling DMF in an argon atmosphere (method A) leads to **5**, an energetically favorable tautomer of **4**. In the presence of air (method B) a mixture of **5** and the oxidation product **6** is generated; a prolonged reaction time furnishes pure **6**.

The structure elucidation for the systems **5** shall be discussed here in detail for **5d**. The ^{1}H-nmr spectrum in DMSO-d$_6$ contains two relatively sharp singlets at δ = 12.04 and 8.18 for 3-H and 8-H and a somewhat broader one for 1-H at δ = 11.41. Irradiation into the singlet of 8-H leads to a positive NOE for the ortho-H of the bromophenyl group (See also Table 1). This is a proof for the bromophenyl substituent on C-7 and altogether for the reaction route $\mathbf{1} + \mathbf{2} \rightarrow \mathbf{3} \rightarrow$ .... Structure **4d** cannot be the final structure, since it contains only two NH groups. The tautomeric constitution **5d** with a proton on C-5 or further tautomeric structures with CH-7 or CH-8a remain. Irradiation into the doublet at δ = 4.55 gives a positive NOE for the *ortho*-H of the phenyl group; that excludes a CH-7 constitution. Single frequency decoupling in the ^{13}C-nmr measurements reveals that the proton signal at 4.55 belongs to the carbon atom at highest field (δ = 37.1); therefore a group CH-8a can also be ruled out, and **5d** is the only remaining structure. The three protons directly connected to the pyridine ring form an AMX spin pattern. The coupling constant between 5-H and 6-H amounts to 5.2 Hz. The olefinic proton 6-H (δ = 5.37) shows a doublet of doublets with a small coupling to 8-H ($|^4J|$ = 1.5 Hz). The NH-8, as mentioned above, leads to a singlet; nevertheless the coupling can be proven by an INDOR experiment. Finally, irradiation into the signal of 6-H provokes in the difference spectrum a positive NOE for the *ortho*-H of the bromophenyl group and a smaller NOE for the *ortho*-H of the phenyl group. The other compounds **5a-c** gave equivalent nmr results.

Such an extended nmr investigation was necessary, because Wawzonek [18] obtained a 2,3,5,6-tetrahydropyrido[2,3-*d*]pyrimidine in the reaction 6-amino-1,3-dimethyluracil and enones like benzalpinacolone. Moreover, Irwine and Wibberley [17] postulate the normal addition direc-

Scheme 1



2	R	method A 5	method B 6
a	H	58%	-
b	OCH_3	55%	-
c	Cl	67%	85%
d	Br	70%	-
e	NO_2	-	80%

tion of the Doebner-v. Miller synthesis in their reaction of 5-aminouracil and crotonaldehyde generating a pyrido[3,2-*d*]pyrimdine.

Compounds **5** are smoothly oxidized to **6**. The sequence **1** + **2** → **5** → **6** can be directly established in an nmr tube using airated DMF/DMSO-d_6 as the solvent. Compounds **6c** and **6e** were isolated in preparative experiments

Table 1. ^{1}H-nmr data of **5a-d** (δ values in DMSO-d_6)

	Pyrido[2,3-d]-pyrimidine					5-Phenyl			7-Aryl		
5	1-H (s)	3-H (s)	8-H (s)	5-H (d)	6-H (dd)	o AA'	m BB'	p C	o AA'	m BB'	p C
a	11.42	12.05	8.17	4.55	5.36	7.26	7.26	7.17	7.46	7.46	7.43
b	11.41	12.02	8.11	4.56	5.22	7.29	7.29	7.16	7.40	7.01	---
									3.77 (OCH_3)		
c	11.41	12.00	8.20	4.56	5.37	7.27	7.27	7.17	7.50	7.50	---
d	11.41	12.04	8.18	4.55	5.37	7.27	7.27	7.16	7.40	7.63	---

Table 2. ^{13}C-nmr data of **5a-d** (δ values in DMSO-d$_6$)

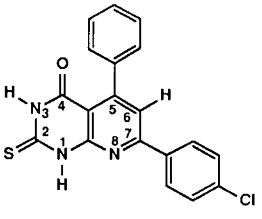
5	Pyrido[2,3-d]-pyrimidine C-2	C-4	C-4a	C-5	C-6	C-7	C-8a	5-Phenyl i	o	m	p	7-Aryl i	o	m	p
a	173.4	160.6	89.7	37.1	104.1	134.1	145.9	146.6	127.5	128.3	126.3	132.7	124.6	128.9	128.8
b	173.3	160.4	89.6	37.0	102.4	132.2	145.7	146.6	127.3	128.2	126.1	126.4	125.8	114.2	159.6
														55.2 (OCH$_3$)	
c	173.4	160.4	89.6	37.0	104.7	133.3	145.7	146.3	127.4	128.2	126.2	131.7	126.3	128.8	132.9
d	173.4	160.5	89.6	37.1	104.7	133.3	145.9	146.3	127.5	128.3	126.3	131.8	126.6	131.8	121.8

Table 3. ^{1}H- and ^{13}C-nmr data of **6c** and **7** (δ-values in DMSO-d$_6$)

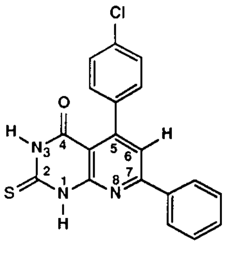
	Pyrido[2,3-d]pyrimidine 1-H	3-H	6-H	Phenyl o-H	m-H	p-H	Chlorophenyl o-H	m-H
6c	12.4	13.1	7.64	8.22	7.53	7.53	7.47	7.47
7	12.4	13.1	7.66	7.4	7.4	7.4	8.25	7.59

	Pyrido[2,3-d]pyrimidine C-2	C-4,7	C-4a	C-5,8a	C-6	Aryl C$_q$	CH	CH(para)
6c	175.4	158.7 159.4	107.9	152.2 152.6	118.9	133.0 136.4 137.1	127.4 127.6 128.9 130.6	130.8
7	175.4	157.9 158.6	108.2	152.6 153.8	119.1	135.3 135.8 138.3	127.4 128.7 128.9 129.4	128.2

(method B) with yields of 85 and 80%, respectively. In order to get a comparison for **6c**, we investigated the reaction of **1** and 3-(4-chlorophenyl)-1-phenyl-2-propen-1-one yielding compound **7**, an isomer of **6c**.



6c



7

The main difference in the nmr data of **6c** and **7** is due to the anisotropy effect of the pyrido[2,3-*d*]pyrimidine skeleton, particularly of its carbonyl group which causes a low-field shift for the protons of the aryl group linked to C-5 (Table 3).

EXPERIMENTAL

Melting points were taken on a Büchi melting point apparatus. The PFT-^{1}H- and ^{13}C-nmr spectra were run on a Bruker AM 400 in DMSO-d$_6$. The mass spectra were recorded on a Varian MAT 711 and a Finnigan M 95 operating at 70 eV.

5,7-Diaryl-2,3,5,8-tetrahydro-2-thioxopyrido[2,3-*d*]pyrimidin-4(1*H*)-ones **5a-d** and 5,7-Diaryl-2,3-dihydro-2-thioxopyrido[2,3-*d*]pyrimidin-4(1*H*)-ones **6c,e**.

General Procedure.

Method A.

A solution of 0.50 g (3.5 mmoles) 6-amino-2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinone (**1**) and 3.5 mmoles of chalcone **2a-d** in 2-3 ml of DMF was refluxed in an argon atmosphere. The reaction can be controlled by tlc on silica gel. After the starting compounds have almost completely disappeared, the solution is cooled down to 5° and the precipitate formed overnight is filtered off.

Method B.

Principally, the same procedure was applied, except the fact that the solution in DMF was refluxed for 15 hours under air.

2,3,6,8-Tetrahydro-5,7-diphenyl-2-thioxopyrido[2,3-*d*]pyrimidin-4(1*H*)-one (**5a**).

The compound was obtained according to method A as yellow crystals, mp 298-300°, yield 0.67 g (58%) [26]. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 333 (32, M$^{+\cdot}$), 332 (40), 331 (100) [27], 330 (61), 256 (16, [M-C$_6$H$_5$]$^+$), 165 (16).

Anal. Calcd. for C$_{19}$H$_{15}$N$_3$OS: C, 68.45; H, 4.53; N, 12.60. Found: C, 68.75; H, 4.28; N, 12.85.

2,3,6,8-Tetrahydro-7-(4-methoxyphenyl)-5-phenyl-2-thioxopyrido[2,3-*d*]pyrimidin-4(1*H*)-one (**5b**).

The compound was isolated according to method A as yellow crystals, mp 300-301°, yield 0.70 g (55%) [26]; ms: (70 eV) m/z (%) = 363 (100, M$^{+\cdot}$), 362 (44), 361 (65) [27], 360 (32), 286 (60,

$[M-C_6H_5]^+$), 243 (17), 143 (22), 135 (29), 134 (34), 133 (33).

Anal. Calcd. for $C_{20}H_{17}N_3O_2S$: C, 66.10; H, 4.72; N, 11.56. Found: C, 66.34; H, 4.41; N, 11.90.

7-(4-Chlorophenyl)-2,3,6,8-tetrahydro-5-phenyl-2-thioxopyrido-[2,3-*d*]pyrimidin-4(1*H*)-one (**5c**).

The compound was obtained according to method A as yellow crystals, mp 299-301°, yield 0.86 g (67%) [26]; ms: (70 eV) m/z (%) = 369 (16)/367 (71) $M^{+\cdot}$, 366 (53), 365 (100) [27], 364 (53), 290 (25, $[M-C_6H_5]^+$), 216 (19), 202 (13), 140 (14), 102 (14).

Anal. Calcd. for $C_{19}H_{14}ClN_3OS$: C, 62.04; H, 3.84; N, 11.42. Found: C, 62.30; H, 3.50; N, 11.58.

7-(4-Bromophenyl)-2,3,6,8-tetrahydro-5-phenyl-2-thioxopyrido-[2,3-*d*]pyrimidin-4(1*H*)-one (**5d**).

The compound was isolated according to method A as yellow crystals, mp 300-301°, yield 1.01 g (70%) [26]; ms: (70 eV) m/z (%) = 413 (48)/411 (100, $M^{+\cdot}$), 410 (55), 409 (62) [27], 408 (27), 336 (24)/334 (24) $[M-C_6H_5]^+$, 216 (13), 183 (13), 103 (13), 102 (19).

Anal. Calcd. for $C_{19}H_{14}BrN_3OS$: C, 55.35; H, 3.42; N, 10.19. Found: C, 55.80; H, 3.30; N, 10.29.

7-(4-Chlorophenyl)-2,3-dihydro-5-phenyl-2-thioxopyrido[2,3-*d*]-pyrimidin-4(1*H*)-one (**6c**).

The compound was obtained according to method B as yellow crystals, mp 345°, yield 1.08 g (85%) [26]. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 367 (38)/365 (100) $M^{+\cdot}$, 216 (18), 165 (23).

Anal. Calcd. for $C_{19}H_{12}ClN_3OS$: C, 62.38; H, 3.31; N, 11.49. Found: C, 62.33; H, 3.35; N, 11.50.

2,3-Dihydro-7-(4-nitrophenyl)-5-phenyl-2-thioxopyrido[2,3-*d*]-pyrimidin-4(1*H*)-one (**6e**).

The compound was obtained according to method B as dark yellow crystals, mp 337-339°, yield 1.05 g (80%); ^{1}H-nmr (DMSO-d_6): δ = 7.43-8.60 (m, 9H, aromatic protons) [28]; ms: (70 eV) m/z (%) = 376 (100, $M^{+\cdot}$), 375 (44), 374 (7), 329 (8), 318 (6), 216 (6), 215 (5).

Anal. Calcd. for $C_{19}H_{12}N_4O_3S$: C, 60.63; H, 3.21; N, 14.89. Found: C, 60.93; H, 3.59; N, 15.11.

5-(4-Chlorophenyl)-2,3-dihydro-7-phenyl-2-thioxopyrido[2,3-*d*]-pyrimidin-4(1*H*)-one (**7**).

The compound was isolated according to method B as pale yellow crystals, mp 310°, yield 1.09 g (85%) [26]; ms: (70 eV) m/z (%) = 367 (37)/365 (100) $M^{+\cdot}$, 364 (50), 307 (7), 216 (15), 202 (9), 182 (9).

Anal. Calcd. for $C_{19}H_{12}ClN_3OS$: C, 62.38; H, 3.31; N, 11.49. Found: C, 62.09; H, 3.60; N, 11.50.

Acknowledgment.

J. Q. thanks the German Academic Exchange Service (DAAD) for the award of a fellowship.

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[26] The ^{1}H- and ^{13}C-nmr data are discussed in the theoretical part.

[27] The peak $[M-2H]^{+\cdot}$ can be either due to a double elimination of H from the molecular ion or to a thermal oxidation process in the ion source.

[28] Compound **6e** is barely soluble in dimethyl sulfoxide or any other solvent normally used for nmr spectroscopy; thus, an unfavorable signal/noise ratio prevented the detection of the broadened NH signals and made the registration of a high resolution ^{13}C-nmr spectrum impossible.