Synthesis of pyrido[2,3-*d*]pyrimidin-7(8*H*)-one derivatives from 5-acetyl-4-aminopyrimidines and β-dicarbonyl compounds

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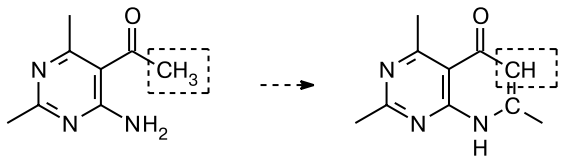
Heating of 5-acetyl-4-aminopyrimidine derivatives with ethyl acetoacetate, ethyl benzoylacetate, and diethyl acetone-1,3-dicarboxylate in the absence of a base gave the corresponding 6-acylpyrido[2,3-*d*]pyrimidin-7(8*H*)-ones. Under analogous conditions, the reaction with ethyl malonate afforded ethyl 7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylates. The pyridone (rather than hydroxypyridine) structures of the pyridopyrimidines obtained were confirmed by IR spectroscopy.

Key words: 2,6-disubstituted 5-acetyl-4-aminopyrimidines, esters of β-oxocarboxylic acids, ethyl malonate, heterocyclization, 6-acylpyrido[2,3-*d*]pyrimidin-7(8*H*)-ones, ethyl 7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylates.

Earlier, we demonstrated that 5-acetyl-4-aminopyrimidine (AAP) derivatives easily prepared from acetylacetone or benzoylacetone[1,2] can be efficiently used to construct the pyrido[2,3-*d*]pyrimidine system.[2—5]

For instance, reactions of some AAP with amide acetals were employed for the synthesis of substituted pyrido[2,3-*d*]pyrimidin-5(8*H*)-ones[2,4] and their condensation with ethyl oxalate afforded the corresponding ethyl 5-oxo-5,8-dihydropyrido[2,3-*d*]pyrimidine-7-carboxylates.[5] The base-catalyzed annelation of the pyridine ring involves the activated methyl group of the starting AAP (Scheme 1).

Scheme 1



At the same time, the pyrido[2,3-*d*]pyrimidine system can be constructed in alternative ways in which AAP derivatives would participate in cyclization as enamino carbonyl components. For example, it is well known that 4-amino-5-formylpyrimidine (AFP) and its derivatives in the presence of a methanolic solution of KOH (or MeONa) undergo the Friedlaender condensation with methylene-reactive ketones to give the corresponding pyrido[2,3-*d*]pyrimidines.[6—8]

However, the behavior of AFP derivatives toward β-dicarbonyl compounds remains unclear. For instance, neither the base- nor acid-catalyzed reaction of acetylacetone or ethyl acetoacetate with 4-amino-5-formyl-2-methoxypyrimidine gave condensation products.[8]

In this study, we tried to obtain new pyrido[2,3-*d*]pyrimidines by reactions of AAP derivatives with esters of β-oxocarboxylic acids. We sought to avoid using base catalysts since pyrimidines of the AAP type, in contrast to AFP, can undergo the Friedlaender self-condensation even in boiling EtOH in the presence of EtONa.[5]

We found that heating (180—190 °C) of pyrimidines **1a—c** with an excess of ethyl acetoacetate or ethyl benzoylacetate (**2**, **3**) without a catalyst gives the corresponding 6-acyl-5-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-ones (**5a—c**, **6a,b**) (their yields are specified in Table 1). Analogously, pyridopyrimidines (**7a,b**) were obtained from compounds **1a,b** and diethyl acetone-1,3-dicarboxylate (**4**) (Scheme 2).

Therefore, closure of the pyridine ring involves detachment of EtOH from oxo esters **2—4** (classic version of the Friedlaender condensation would yield ethyl pyrido[2,3-*d*]pyridine-6-carboxylates **8—10**, which were not detected in the reaction mixtures).

The structures of the pyridopyrimidines obtained were confirmed by spectroscopic data. Their mass spectra contain molecular ion peaks (see Table 1). The ^{1}H NMR spectra of compounds **5** and **6** show no signals for the protons of the ethoxy group but contain a signal for the NH group. Hence, the spectra of the pyridopyrimidines synthesized from dicarboxylate **4** correspond to structure **7** with a single ethoxycarbonyl group (Table 2).

It is well known that the tautomeric equilibrium 2-pyridone $\rightleftharpoons$ 2-hydroxypyridine in the crystalline

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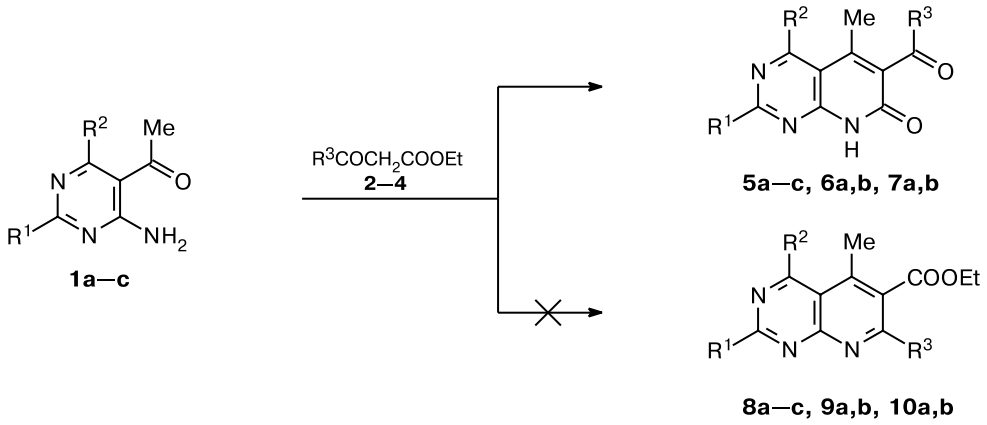
Table 1. Yields, melting points, elemental analysis data, and mass spectra of compounds **5—7**, **11**, and **12**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)				Molecular formula	MS, m/z (I_{rel} (%))
			C	H	N	S		
5a	78	291—292	69.65 69.61	5.33 5.15	14.43 14.33	—	$C_{17}H_{15}N_3O_2$	293 $[M]^{+\bullet}$ (100), 292 $[M - H]^+$ (77), 278 $[M - Me]^+$ (67)
5b	72	319—320	62.78 62.75	4.70 4.65	13.32 12.91	9.61 9.85	$C_{17}H_{15}N_3O_2S$	325 $[M]^{+\bullet}$ (11), 310 $[M - Me]^+$ (100), 292 $[M - SH]^+$ (30)
5c*	74	299—301	62.32 62.29	4.34 4.30	12.91 12.82	—	$C_{17}H_{14}ClN_3O_2$	327 $[M]^{+\bullet}$ (100), 312 $[M - Me]^+$ (37)
6a	83	303—304	74.00 74.35	4.97 4.82	11.49 11.82	—	$C_{22}H_{17}N_3O_2$	355 $[M]^{+\bullet}$ (76), 354 $[M - H]^+$ (100), 326 $[M - H - CO]^+$ (59)
6b	95	334—336	68.40 68.20	4.58 4.42	10.88 10.85	8.07 8.27	$C_{22}H_{17}N_3O_2S$	387 $[M]^{+\bullet}$ (49), 386 $[M - H]^+$ (73), 372 $[M - Me]^+$ (100), 358 $[M - H - CO]^+$ (32), 354 $[M - SH]^+$ (37), 310 $[M - Ph]^+$ (16), 294 $[M - H - Me - Ph]^+$ (42), 105 (68), 77 (70), 59 (73)
7a	54	171—172	65.60 65.74	5.31 5.24	11.55 11.50	—	$C_{20}H_{19}N_3O_4$	365 $[M]^{+\bullet}$ (24), 319 $[M - C_2H_5OH]^+$ (33), 293 $[M - C_2H_4 - CO_2]^+$ (49), 292 $[M - C_2H_5O - CO]^+$ (43), 291 $[M - C_2H_5OH - CO]^+$ (57), 278 $[M - CH_2COOC_2H_5]^+$ (100)
7b	74	207—208	60.48 60.44	4.71 4.82	10.81 10.57	7.93 8.07	$C_{20}H_{19}N_3O_4S$	397 $[M]^{+\bullet}$ (8), 382 $[M - Me]^+$ (12), 364 $[M - SH]^+$ (6), 336 $[M - Me - C_2H_5OH]^+$ (78), 310 $[M - CH_2CO_2C_2H_5]^+$ (62), 294 $[M - Me - C_2H_5OH - CH_2CO]^+$ (100)
11	39	184—185	73.32 73.67	5.19 5.29	16.05 16.37	—	$C_{21}H_{18}N_4O$	342 $[M]^{+\bullet}$ (54), 237 $[M - PhCH_2N - CO]^+$ (27), 106 $[PhCH_2NH]^+$ (100), 91 $[PhCH_2]^+$ (60)
12a	82	216—217	66.77 66.86	5.42 5.30	13.15 13.00	—	$C_{18}H_{17}N_3O_3$	323 $[M]^{+\bullet}$ (73), 278 $[M - C_2H_5O]^+$ (83), 277 $[M - C_2H_5OH]^+$ (53), 251 $[M - C_2H_4 - CO_2]^+$ (100), 223 $[M - C_2H_4 - CO_2 - CO]^+$ (35)
12b	85	271—272	60.52 60.83	4.98 4.82	11.78 11.82	8.84 9.02	$C_{18}H_{17}N_3O_3S$	355 $[M]^{+\bullet}$ (12), 340 $[M - Me]^+$ (27), 322 $[M - SH]^+$ (9), 310 $[M - C_2H_5O]^+$ (12), 294 $[M - Me - C_2H_5OH]^+$ (100)

* Found (%): Cl, 11.07. Calculated (%): Cl, 10.82.

Scheme 2



R^1 = Ph, R^2 = Me (**a**), SMe (**b**); R^1 = 4-ClC_6H_4, R^2 = Me (**c**); R^3 = Me (**2**, **5**, **8**), Ph (**3**, **6**, **9**), CH_2COOEt (**4**, **7**, **10**)

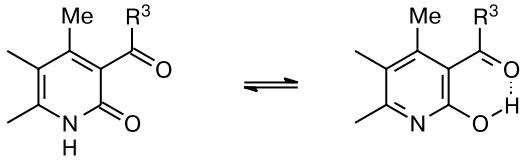
Table 2. ^{1}H NMR spectra of compounds **5**—**7**, **11**, and **12**

Compound	Solvent	δ (*J*/Hz)					
		4-Me (s, 3 H)	5-Me (s, 3 H)	SMe (s, 3 H)	NH (br.s, 1 H)	Ar	Other signals
5a	$CDCl_3$	3.01	2.61	—	9.25	7.52 (m, 3 H); 8.50 (m, 2 H)	2.61 (s, 3 H, COMe)
5b	DMSO-d_6	—	2.58	2.79	12.50	7.58 (m, 3 H); 8.48 (m, 2 H)	2.44 (s, 3 H, COMe)
5c	DMSO-d_6	2.97	2.50	—	12.50	7.62, 8.43 (both d, 2 H each, J = 7.5)	2.47 (s, 3 H, COMe)
6a	$CDCl_3$	3.02	2.52	—	9.18	7.42—7.68 (m, 6 H); 7.97, 8.51 (both m, 2 H each)	—
6b	DMSO-d_6	—	2.50	2.78	12.72	7.58 (m, 5 H);7.72 (m, 1 H); 7.96, 8.50 (both m, 2 H each)	—
7a*	$CDCl_3$	3.01	2.68	—	9.57	7.52 (m, 3 H); 8.50 (m, 2 H)	1.27 (t, 3 H, C$\underline{H}_3$CH$_2$, J = 6.8); 4.08 (s, 2 H, CH$_2$); 4.19 (q, 2 H, C$\underline{H}_2$CH$_3$, J = 6.8)
7b**	$CDCl_3$	—	2.81	2.81	9.54	7.52 (m, 3 H); 8.49 (m, 2 H)	1.25 (t, 3 H, C$\underline{H}_3$CH$_2$, J = 6.8); 4.08 (s, 2 H, CH$_2$); 4.20 (q, 2 H, C$\underline{H}_2$CH$_3$, J = 6.8)
11	$CDCl_3$	—	2.62	—	6.02 (N$\underline{H}$CH$_2$); 9.25	7.20—7.60 (m, 8 H); 8.43 (m, 2 H)	4.97 (d, 2 H, CH$_2$, J = 5.0); 6.31 (s, 1 H, H(6))
12a	$CDCl_3$	3.00	2.64	—	9.70	7.50 (m, 3 H); 8.50 (m, 2 H)	1.42 (t, 3 H, C$\underline{H}_3$CH$_2$, J = 6.8); 4.48 (q, 2 H, CH$_2$, J = 6.8)
12b	$CDCl_3$	—	2.82	2.78	9.30	7.52 (m, 3 H); 8.49 (m, 2 H)	1.41 (t, 3 H, C$\underline{H}_3$CH$_2$, J = 6.8); 4.48 (q, 2 H, CH$_2$, J = 6.8)

* The signals for the enol form (12%): 1.32 (t, 3 H, C$\underline{H}_3$CH$_2$, J = 6.8 Hz); 2.62 (s, 3 H, 5-Me); 4.28 (q, 2 H, C$\underline{H}_2$CH$_3$, J = 6.8 Hz); 5.35 (s, 1 H, HC=); 9.40 (br.s, 1 H, NH); 12.40 (br.s, 1 H, OH); the other signals are identical for both forms.
** The signals for the enol form (13%): 1.32 (t, 3 H, C$\underline{H}_3$CH$_2$, J = 6.8 Hz); 2.62 (s, 3 H, 5-Me); 2.74 (s, 3 H, SMe); 4.28 (q, 2 H, C$\underline{H}_2$CH$_3$, J = 6.8 Hz); 5.35 (s, 1 H, HC=); 9.38 (br.s, 1 H, NH); 12.35 (br.s, 1 H, OH); the other signals are identical for both forms.

state and in neutral solvents (under not very high dilution) is usually shifted to the oxo form virtually completely.[9—11] Nevertheless, it seemed to us that the hydroxy tautomer of the pyridopyrimidines obtained can be stabilized by an intramolecular O—H...O=C hydrogen bond (Scheme 3).

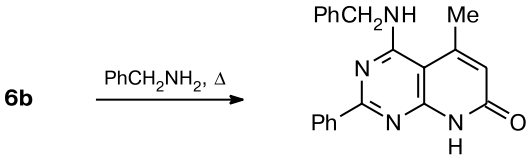
Scheme 3



However, the IR spectra of samples (both as pellets with KBr and in $CHCl_3$) provide evidence for the pyridone structure. For instance, the IR spectrum of compound **6a** in $CHCl_3$ shows a narrow band of the free NH group (3380 cm^{-1}) and a characteristic ν(CO) band of the amide fragment (1664 cm^{-1}). The intense absorption band at 1680 cm^{-1} was assigned to the benzoyl CO group. The IR spectrum for pellets in KBr also exhibit the corresponding bands of the C=O stretching vibrations at 1648 and 1680 cm^{-1}. Similar spectral patterns were observed for the other pyridopyrimidines obtained (Table 3).

The lactam structure of compounds **5**—**7** can also be confirmed by the IR spectra of 4-benzylamino-5-methyl-2-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11**) obtained in moderate yield by a reaction of 4-methylthiopyridopyrimidine **6b** with boiling benzylamine (Scheme 4).

Scheme 4



11

In this case, the replacement of the methylthio group by the benzylamino one (*cf.* Refs 12, 13) is accompanied by debenzoylation (^{1}H NMR spectra of compound **11** in $CDCl_3$ show a singlet at δ 6.31 for the H(6) proton of the bicycle). It is worth noting that the amide fragment in compound **11**, in which the hydroxypyridine structure cannot be stabilized by intramolecular hydrogen bonding,

Table 3. Vibrational frequencies in the IR spectra of compounds **5—7**, **11**, and **12**

Compound	Conditions*	ν/cm^{-1}			
		N—H**	C=O amide	C=O	C=N, C=C
5a	$CHCl_3$	3384	1668	1700	1592, 1572, 1524
	KBr	3200—2600	1660	1700	1592, 1568, 1524
5b	KBr	3200—2600	1664	1692	1592, 1568, 1512
5c	KBr	3200—2800	1664	1696	1588, 1568, 1520
6a	$CHCl_3$	3380	1664	1680	1596, 1568, 1528
	KBr	3200—2600	1648	1684	1596, 1572, 1524
6b	KBr	3200—2700	1640	1684	1588, 1564, 1512
7a	$CHCl_3$	3380	1668	1732, 1704	1592, 1572, 1524
	KBr	3200—2600	1648	1740, 1704	1592, 1568, 1520
7b	$CHCl_3$	3376	1668	1736, 1704	1580, 1564, 1516
	KBr	3200—2700	1664	1736, 1692	1580, 1568, 1516
11	$CHCl_3$	3388, 3504 ($NHCH_2$)	1668	—	1604, 1576, 1548
	KBr	3200—2600, 3500 ($NHCH_2$)	1656	—	1604, 1572, 1544
12a	$CHCl_3$	3376	1672	1728	1600, 1572, 1524
	KBr	3300—2900	1672	1716	1600, 1572, 1532
12b	KBr	3200—2700	1644	1724	1592, 1556, 1516

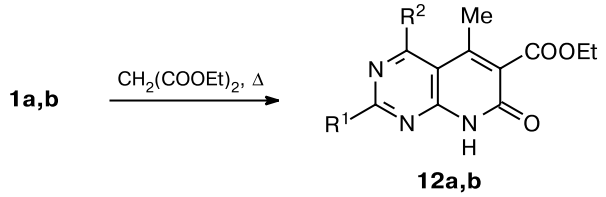
* Recording conditions.

** The NH frequency range in the IR spectra (KBr) shows a complicated absorption pattern (including overlap with bands of CH) with a peak at 3000 to 2800 cm^{-1} (for compound **12a**, at 3250 to 3150 cm^{-1}).

absorbs at the same frequencies as that in compounds **5—7** (IR ($CHCl_3$), cm^{-1}: 3388 (NH), 1668 (CO)).

We also used AAP derivatives as enamino carbonyl reagents in reactions with ethyl malonate. Under the same conditions as with β-oxo esters, ethyl 7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylates **12a,b** were obtained from pyrimidines **1a,b** in 82 to 85% yields (Scheme 5).

Scheme 5



R^1 = Ph, R^2 = Me (**a**), SMe (**b**)

The structures of compounds **12a,b** were confirmed by mass and ^{1}H NMR spectra. In the IR spectrum of compound **12a** in $CHCl_3$, the absorption bands of the amide fragment appear at 3376 (NH) and 1672 cm^{-1} (C=O).*

Experimental

^{1}H NMR spectra were recorded on a Bruker WM-250 instrument. IR spectra were recorded on a Specord M-80 instrument. Mass spectra were recorded on a Kratos MS-30 instrument (EI, 70 eV, ionization chamber temperature 250 °C, direct inlet probe).

Pyrimidines **1a**,[1] **1b**,[2] and **1c**[5] were prepared according to known procedures.

6-Acetyl-2-aryl-4,5-dimethylpyrido[2,3-*d*]pyrimidin-7(8*H*)-ones (5a,c) and 6-acetyl-5-methyl-4-methylthio-2-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (5b) (general procedure). A mixture of the corresponding pyrimidine **1** (1 mmol) and ethyl acetoacetate (2.6 mL, 20 mmol) was refluxed for 4 h and cooled to 20 °C. The precipitate that formed was filtered off and washed with MeCN (10 mL) to give colorless pyridopyrimidinones **5a—c** (yields, melting points, elemental analysis data, and mass spectra are given in Table 1; ^{1}H NMR and IR spectra are presented in Tables 2 and 3, respectively).

6-Benzoyl-4,5-dimethyl-2-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (6a) and 6-benzoyl-5-methyl-4-methylthio-2-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (6b). A mixture of pyrimidine **1a** or **1b** (1 mmol) and ethyl benzoylacetate (2.3 mL, 13 mmol) was heated in an oil bath at 180 to 190 °C for 5 h and then cooled to 20 °C. The precipitate that formed was filtered off and washed with benzene—light petroleum (1 : 1) (10 mL) to give lemon yellow and colorless pyridopyrimidinones **6a,b**, respectively (see Tables 1—3).

Ethyl 3-[(4,5-dimethyl- and 5-methyl-4-methylthio)-7-oxo-2-phenyl-7,8-dihydropyrido[2,3-*d*]pyrimidin-6-yl]-3-oxopropionates (7a,b). A mixture of pyrimidine **1a** or **1b** (1 mmol) and diethyl acetone-1,3-dicarboxylate (2.4 mL, 13 mmol) was heated in an oil bath at 180 to 190 °C for 5 h and then cooled to 20 °C. The precipitate that formed was filtered off and washed with benzene—light petroleum (1 : 2) (6 mL) for **7a** and MeCN (10 mL) for **7b** to give pale yellow and colorless esters **7a,b**, respectively (see Tables 1—3).

4-Benzylamino-5-methyl-2-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (11). A mixture of pyridopyrimidinone **6b** (0.1 g, 0.26 mmol) and benzylamine (2 mL, 18.3 mmol) was refluxed for 6 h, diluted with benzene—light petroleum (1 : 4, 10 mL), brought to boiling, and then cooled to 20 °C. The precipitate that formed upon trituration was filtered off to give colorless pyridopyrimidinone **11** (0.034 g, 39%) (see Tables 1—3).

Ethyl (4,5-dimethyl- and 5-methyl-4-methylthio)-7-oxo-2-phenyl-7,8-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylates (12a,b). A mixture of pyrimidine **1a** or **1b** (1 mmol) and ethyl malonate (2.6 mL, 17 mmol) was refluxed for 5 h and cooled to 20 °C. The precipitate that formed was filtered off and recrystallized from MeCN to give colorless compound **12a** or the

* Earlier,[8] some 4-amino-5-formyl-2-methoxypyrimidines have been reported to react with ethyl malonate, though only in the presence of MeONa, and the hydroxypyridine structure has been assigned to the compounds obtained.

precipitate was heated with MeCN (10 mL) to boiling, cooled to 20 °C, and filtered off to give colorless ester **12b** (see Tables 1—3).

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