Pyridazines; XXX[1,2]. A Novel Approach to Pyrido[2,3-*d*]pyridazines by Annelation of the Pyridine Ring to the 1,2-Diazine System

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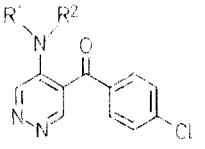
Procedures for high-yield syntheses of 2-ethoxy- and 2-dimethylamino-4-arylpyrido[2,3-*d*]pyridazines (**3a, b, 5**), 3-alkyl- and 1-alkyl-4-aryl-1,2-dihydro-2-oxopyrido[2,3-*d*]pyridazines (**4b, 6**) as well as ethyl 4-aryl-1,2-dihydro-2-oxopyrido[2,3-*d*]pyridazine-3-carboxylates (**7a, b**) starting from 5-amino-4-pyridazinyl aryl ketones (**1a, b**) are reported. Considerable variability of the substitution pattern in the pyridine moiety of this bicyclic system is provided by the proposed strategy of annelation of the pyridine ring to a preformed pyridazine nucleus.

As an extension of our previous investigations[1,3,4] directed toward the synthesis of heterocycle-annelated pyridazines as building blocks for the preparation of potentially biologically active compounds, 4-arylpyrido[2,3-*d*]pyridazines became an object of interest. Various biological activities, e.g. an interesting diuretic effect[5,6], have been observed with derivatives of pyrido[2,3-*d*]pyridazines. Synthesis of this ring system is usually achieved by cyclization reactions of appropriately 2,3-disubstituted pyridines[7,8]. To our knowledge, the only exception to this general route so far reported consists of a [4+2] cycloaddition reaction of lactim ethers with 1,2,4,5-tetrazine-3,6-dicarboxylic esters[9].

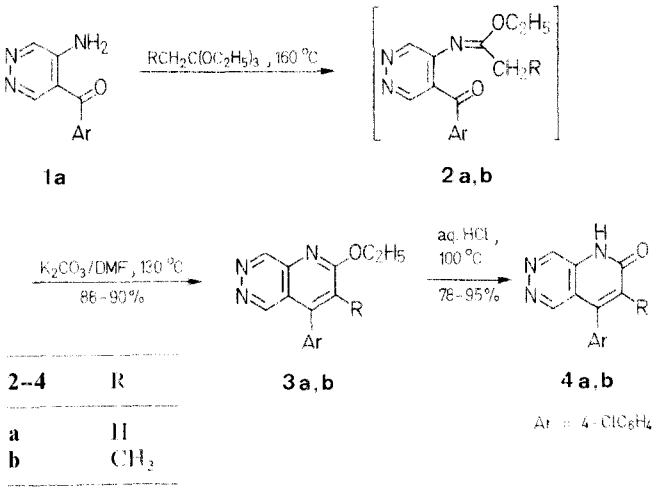
We now wish to describe high-yield reaction sequences starting from 5-amino-4-pyridazinyl aryl ketones[10,11], which lead to 4-arylpyrido[2,3-*d*]pyridazines bearing various substituents at N-1, C-2, and C-3.



1a-d

1	R^1	R^2
a	H	H
b	CH_3	H
c	H	$COCH_3$
d	CH_3	$COCH_3$

The recently reported imido esters **2a, b**[11], easily available from the amino ketone **1a**[10,12], seemed to be suitable precursors to the target compounds, since we anticipated a sufficient degree of acidity of the CH_2 moiety adjacent to the carboxylic carbon atom. In fact, conversion of **2a** into 4-(4-chlorophenyl)-2-ethoxypyrido[2,3-*d*]pyridazine (**3a**) can be accomplished simply by heating **2a** in dimethyl formamide solution in the presence of potassium carbonate. By refluxing in 6 normal hydrochloric acid, **3a** can be hydrolyzed to **4a** in high yield (Scheme **A**).

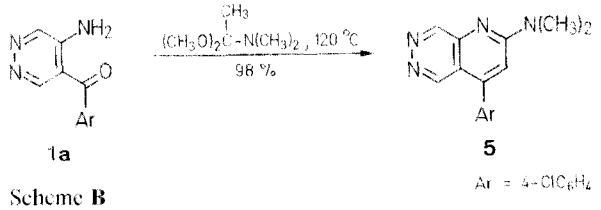


1a **2a,b** **3a,b** **4a,b**

2–4	R
a	H
b	CH_3

Scheme A

In contrast, **3a** was found to withstand aminolysis, as shown from unsuccessful attempts to prepare 4-arylpyrido[2,3-*d*]pyridazines bearing dialkylamino groups at C-2 by treatment of **3a** with secondary amines. In addition, we did not succeed in converting the pyridone **4a** into a 2-chloro-compound, as **4a** on treatment with phosphorus oxychloride/pyridine only afforded intractable tars. However, condensation of amino ketones like **1a** with dimethylacetamide dimethyl acetal provides a convenient route to 4-aryl-2-dimethylaminopyrido[2,3-*d*]pyridazines like **5** (Scheme **B**).



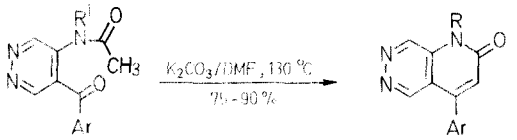
1a **5**

Scheme B

The procedure outlined in Scheme **A** also permits an easy access to 3-alkyl-1,2-dihydro-2-oxopyrido[2,3-*d*]pyridazines, as shown by the conversion of **1a** to **4b** *via* **2b** and **3b**. This reaction sequence, of course, is not suitable for the preparation of the corresponding N-1-alkyl derivatives.

Furthermore, based on previous observations[4,11], attempts to directly alkylate compounds of type **4a** are expected to result in preferential attack at the pyridazine nucleus (N-6). This problem could be overcome by employing *N*-alkylamides like **1d**[11], easily available from **1a** *via* imidates **2**[11], as shown by the preparation of compound **6** in 90% yield (based on **1d**).

It is of interest to note that secondary *N*-(5-aroyl-4-pyridazinyl)amides like **1c**[11] also cyclize smoothly on treatment with potassium carbonate in dimethyl formamide at 130°C, thus giving rise to another high-yield route to 4-aryl-1,2-dihydro-2-oxopyrido[2,3-*d*]pyridazines (Scheme **C**).

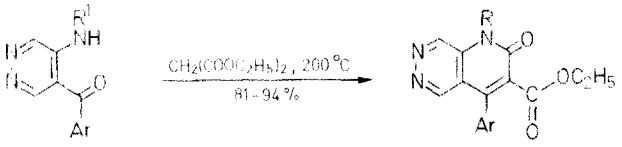


1c,d → **4a** R = H; **6** R = CH_3; Ar = 4-ClC_6H_4

Scheme **C**

Compared to the reaction sequence **1a** → **2** → **3** → **4** (Scheme A), which is limited in scope by the availability of the appropriate ortho esters, the latter procedure should also represent a versatile alternative for the synthesis of 4-aryl-1,2-dihydro-2-oxopyrido[2,3-*d*]pyridazines bearing various substituents at C-3, since the required amides are easily obtained[11].

Furthermore, it was found that the highly activated methylene group of diethyl malonate permits the facile one-step conversion of **1a** as well as of **1b** into 4-aryl-1,2-dihydro-2-oxopyrido[2,3-*d*]pyridazines with a carboxylic ester function at C-3 (compounds **7a, b**; Scheme **D**).



1a,b → **7a,b**; Ar = 4-ClC_6H_4

7	R
a	H
b	CH_3

Scheme **D**

The IR- and ^{1}H-NMR-spectroscopic data displayed in the Table are in full agreement with the structures proposed for the novel compounds **3–7**. Occurrence of $\nu_{C=O}$ vibration bands at 1670–1680 cm^{-1} in the IR spectra of **4a, b** and **7a** suggests that these compounds are best formulated as 2(1*H*)pyridones. The marked differences in the H-5 chemical shifts between compounds **3a, 4a** and their 3-methyl derivatives **3b, 4b** is best interpreted in terms of non-coplanarity of the triazanaphthalene system and the aryl moiety in the latter compounds due to the steric requirements of the substituent attached to C-3.

In summary, in contrast to synthetic routes to pyrido[2,3-*d*]pyridazines reported until now, the proposed strategy of annelation of the pyridine nucleus to the pyridazine system by N-1/C-2 and C-3/C-4 bond formation, similar to Friedländer-type quinoline syntheses[13], offers a high degree of variability with respect to substituents attached to

Table. Pyrido[2,3-*d*]pyridazines (**3–7**) Prepared

Product	Yield [%]	m.p. [°C]	Molecular Formula[a]	IR (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-NMR δ [ppm]
3a	88[b]	145–147	$C_{15}H_{12}ClN_3O$ (285.7)	–	1.50 (t, J = 7 Hz, 3H, OCH_2CH_3); 4.70 (q, J = 7 Hz, 2H, OCH_2CH_3); 7.20 (s, 1H, H-3); 7.45–7.70 (AA'BB', J = 9 Hz, 4H, C_6H_4Cl); 9.45, 9.65 (2d, J = 1.5 Hz, 1H each, H-5, H-8)[f]
3b	90[b]	195–196	$C_{16}H_{14}ClN_3O$ (299.8)	–	1.50 (t, J = 7 Hz, 3H, OCH_2CH_3); 2.20 (s, 3H, 3-CH_3); 4.70 (q, J = 7 Hz, 2H, OCH_2CH_3); 7.20–7.65 (AA'BB', J = 9 Hz, 4H, C_6H_4Cl); 8.95, 9.55 (2d, J = 1.5 Hz, 1H each, H-5, H-8)[f]
4a	78[c] 75[d]	315–330 (decomp.)	$C_{13}H_8ClN_3O \cdot 1/2\,H_2O$ (266.7)	1680	6.85 (s, 1H, H-3); 7.65 (s, 4H, C_6H_4Cl); 9.05, 9.30 (2d, J = 1.5 Hz, 1H each, H-5, H-8); 12.50 (broad, 1H, NH)[g]
4b	95[c]	310–330 (decomp.)	$C_{14}H_{10}ClN_3O \cdot 1/4\,H_2O$ (276.2)	1680	1.95 (s, 3H, CH_3); 7.40–7.75 (AA'BB', J = 9 Hz, 4H, C_6H_4Cl); 8.55, 9.25 (2d, J = 1.5 Hz, 1H each, H-5, H-8); 11.50–13.50 (very broad, 1H, NH)[g]
5	98[b]	260–262	$C_{15}H_{13}ClN_4$ (284.7)	–	3.65 (s, 6H, CH_3); 7.65 (s, 4H, C_6H_4Cl); 7.75 (s, 1H, H-3); 9.70, 10.00 (2d, J = 1.5 Hz, 1H each, H-5, H-8)[h]
6	90[c]	258–260	$C_{14}H_{10}ClN_3O$ (271.7)	1660	3.75 (s, 3H, CH_3); 7.00 (s, 1H, H-3); 7.65 (s, 4H, C_6H_4Cl); 9.05, 9.75 (2d, J = 1.5 Hz, 1H each, H-5, H-8)[g]
7a	94[b]	214–220	$C_{16}H_{12}ClN_3O_3$ (329.7)	1730, 1670	1.00 (t, J = 7 Hz, 3H, OCH_2CH_3); 4.05 (q, J = 7 Hz, 2H, OCH_2CH_3); 7.45–7.75 (AA'BB', J = 9 Hz, 4H, C_6H_4Cl); 8.75, 9.30 (2d, J = 1.5 Hz, 1H each, H-5, H-8); 13.00 (broad, 1H, NH)[g]
7b	81[b]	194–197	$C_{17}H_{14}ClN_3O_3$ (343.8)	1730, 1655	1.00 (t, J = 7 Hz, 3H, OCH_2CH_3); 3.80 (s, 3H, NCH_3); 4.10 (q, J = 7 Hz, 2H, OCH_2CH_3); 7.45–7.75 (AA'BB', J = 9 Hz, 4H, C_6H_4Cl); 8.80, 9.80 (2d, J = 1.5 Hz, 1H each, H-5, H-8)[g]

[a] Satisfactory microanalyses obtained: C ± 0.28, H ± 0.16, N ± 0.29
[b] Yield based on starting amino ketone
[c] Yield based on final reaction step
[d] Yield based on **3a**
[d] Yield based on **1c**
[f] $CDCl_3$ (TMS)
[g] DMSO-d_6 (TMS)
[h] D_2O/DCl [$(CH_3)_3Si(CD_2)_3SO_3Na$]

positions N-1, C-2, and C-3 of this ring system. Additionally, it should be mentioned that the substituents in the phenyl moiety can also be varied within a wide range, since the first reaction step in the preparation of the starting amino ketones consists of a Minisci-type aroylation[14] of 4-pyridazinecarboxylic acid.

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were obtained using a Jasco IRA-1. ^{1}H-NMR spectra were recorded on a Varian EM 390 (90 MHz). Microanalyses were carried out at the Institute of Physical Chemistry, University of Vienna, by Dr. J. Zak.

2-Ethoxypyrido[2,3-*d*]pyridazines 3a, b; General Procedure:
A mixture of the amino ketone **1a**[10] (233 mg, 1 mmol) and the appropriate ortho ester (triethyl orthoacetate or -propionate, respectively; 10 ml) is heated to 160°C for 6 h. After concentration under reduced pressure, the oily residue is dissolved in dry dimethylformamide (10 ml); potassium carbonate (138 mg, 1 mmol) is added, and the mixture is heated to 130°C for 2 h. The residue obtained after removal of the solvent is extracted with boiling toluene (2 × 50 ml). Concentration gives the crude products, which are purified by recrystallization from toluene/light petroleum (b.p. 50–70°C) (for **3a**) or acetone (for **3b**), to give colorless crystals.

Hydrolysis of 3a, b to 4a, b; General Procedure:
A solution of the ethoxy compound **3a** or **3b**, (1 mmol) in 6 normal hydrochloric acid (20 ml) is refluxed for 2 h. After cooling, the pH is adjusted to 3–4 by addition of 2 normal sodium hydroxide. The precipitate is collected and washed with water. Recrystallization from 1-butanol gives the pure products as colorless crystals.

4-(4-Chlorophenyl)-2-dimethylaminopyrido[2,3-*d*]pyridazine (5):
A mixture of the amino ketone **1a**[10] (233 mg, 1 mmol) and dimethylacetamide dimethyl acetal (5 ml) is heated to 120°C for 2 h. The residue obtained by evaporation of volatile components is recrystallized from ethanol to give the pure product as colorless crystals.

1,2-Dihydro-2-oxopyrido[2,3-*d*]-pyridazines 4a, 6 from Amides 1c, d:
To a solution of the amide **1c**[11] or **1d**[11], (1 mmol) in dry dimethylformamide (10 ml) is added potassium carbonate (138 mg, 1 mmol), and the mixture is heated to 130°C for 2 h. After concentration, the residue is treated with water (20 ml).

In the case of **4a**, the pH is adjusted to 3–4 by addition of 2 normal hydrochloric acid, and the precipitated solid is collected, washed with water, and recrystallized (see above).

In the case of **6**, the aqueous suspension is extracted with dichloromethane. The residue obtained by concentration of the extract is recrystallized from ethanol to give colorless needles.

1,2-Dihydro-2-oxopyrido[2,3-*d*]pyridazine-3-carboxylic esters 7a, b:
A mixture of the amino ketone **1a**[10] or **1b**[11] (1 mmol) and diethyl malonate (10 ml) is heated to 200°C for 2 h. The reagent is removed by bulb-to-bulb (Kugelrohr) distillation (0.076 torr, 70°C), and the residue is recrystallized from ethanol/water (for **7a**) or toluene (for **7b**), to give the pure products as pale yellow crystals.

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[2] Presented in part at the 10th International Congress of Heterocyclic Chemistry, Waterloo, Ontario, Canada, 1985, and at the Scientific Meeting of the "Deutsche Pharmazeutische Gesellschaft", Braunschweig, West Germany, 1985.

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Note added in proof: For a recent application of amide acetals in syntheses of heterocycle-annelated 2-dialkylaminopyridines cf. Eiden, F., Berndl, K. *Arch. Pharm. (Weinheim, Ger.)* **1986**, *319*, 347.