5-Acetyl-2-methyl-4-nitro-6-phenyl-3(2*H*)-pyridazinone: Versatile Precursor to Hetero-Condensed Pyridazinones

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The title compound **2** was found to be a very useful intermediate to synthesize five- and six-membered hetero-condensed pyridazinones in high yields under generally mild and simple reaction conditions.

3(2*H*)-Pyridazinones have aroused great interest in the past few years due to their application in agriculture as herbicides[1] and in medicine as cardiovascular drugs.[2] In a previous paper we reported the synthesis of the title compound **2**, easily available in moderate yield through oxidative cleavage of the isoxazolo[3,4-*d*]pyridazinone **1** by ceric ammonium nitrate (CAN).[3] Compound **1**, in turn, was obtained in almost quantitative yield by cyclocondensation of the suitable 3,4-difunctionalized isoxazole with methyl hydrazine.[4] In compounds of type **2**, the nitro group is a very good leaving group and easily undergoes substitution by *O*-,*N*-, and *S*-nucleophiles.[5-7] We have previously exploited the high reactivity of the 5-acetyl-4-nitro-3(2*H*)-pyridazinone **(2)** to synthesize 1*H*- and 2*H*-pyrazolo[3,4-*d*]pyridazinones by treatment with hydrazine (methylhydrazine) and phenylhydrazine, respectively.[8] In addition we have demonstrated that **2** behaves as the dienophilic counterpart in [2 + 4] Diels–Alder cycloadditions to afford dihydro- and tetrahydrophthalazinones.[9]

Stimulated by the appearance of a review in the literature by Haider and Heinisch on the cyclocondensation of a variety of heteroaromatics on the 1,2-diazine system,[10] we report here the results of our studies in this field, using compound **2** as the precursor.

Reaction of **2** with ethyl thioglycolate anion in alcoholic medium at room temperature smoothly afforded the ethyl thieno[2,3-*d*]pyridazine-2-carboxylate **3** in excellent yield (Scheme 1). Reaction of **2** with sarcosine ethyl ester gave under similar reaction conditions, as expected in view of the lower acidity of the methylene group, the open chain intermediate **4a** in 76% yield. Following the same procedure, condensation of **2** with *N*-methyl-β-alaninenitrile afforded the 4-(2-cyanoethyl)derivative **4b** (83%). Ring closure of **4a** and **4b** to the corresponding pyrrolo[2,3-*d*]pyridazine **5a** and pyrido[2,3-*d*]pyridazine **5b** was easily accomplished in good yields by briefly heating with sodium ethoxide in ethanol. Conversion of **2** into **5a** and **5b** could be directly performed in a single step, without the isolation of the intermediates **4a** and **4b**, in 70 and 85% yields, respectively. The ring closure of **4b** into the isomeric 2-cyanomethylpyrrolo[2,3-*d*]pyridazinone could be excluded, taking into account the major acidity of the methylene neighbouring the cyano group, as well as the cyclocondensations of similar *vic*-substituted pyridazines with the same type of reagent, affording pyridopyridazines.[11] Moreover, niether of the two signals for NCH_3 groups overlap at $\delta = 3.77$ in the ^1H NMR spectrum, which could be attributed to the *N*-methylpyrrole moiety. In fact both the signals found for this type of NCH_3 in

Table. Compounds **3–8** and **11** Prepared

Product[a]	mp (°C) (solvent)	Yield (%)	IR (Nujol) ν (cm^{-1})	^1H NMR ($CDCl_3$)[b] δ, J (Hz)
3	182–183 (EtOH)	79[c]	1740 (COOEt), 1670[g]	1.40 (t, 3H, OCH_2CH_3, J = 7.0), 2.12 (s, 3H, CH_3C), 3.91 (s, 3H, NCH_3), 4.38 (q, 2H, OCH_2CH_3, J = 7.0), 7.40–7.60 (m, 5H, C_6H_5)
4a	112–114 (cyclohexane)	76[c]	1750 (COOEt), 1690,[h] 1645[g]	1.30 (t, 3H, OCH_2CH_3, J = 7.0), 2.15 (s, 3H, $COCH_3$), 2.92 (s, 3H, 4-NCH_3), 3.79 (s, 3H, 2-CH_3), 4.25 (q, 2H, OCH_2CH_3, J = 7.0), 7.30–7.50 (m, 5H, C_6H_5)
4b	95 ($EtOH/H_2O$)	83[c]	2250 (CN), 1690,[h] 1640[g]	2.07 (s, 3H, $COCH_3$), 2.77 (t, 2H, NCH_2, J = 7.1), 2.83 (s, 3H, 4-NCH_3), 3.82 (s, 3H, 2-CH_3), 3.86 (t, 2H, CH_2CN, J = 7.1), 7.30–7.45 (m, 5H, C_6H_5)
5a	275 (dec) (EtOH)	70[c]	3700–3100 (OH), 1730 (COOH), 1640[g]	2.05 (s, 3H, CH_3C), 3.77 (s, 3H, NCH_3, pyridazine), 4.52 (s, 3H, NCH_3, pyrrole), 7.47 (s, 5H, C_6H_5)
5b	171–172 (EtOH)	85[c]	2230 (CN), 1665[g]	1.64 (s, 3H, CCH_3), 3.75 (s, 3H, NCH_3), 3.78 (s, 3H, NCH_3), 3.92 (s, 2H, CH_2), 7.42 (s, 5H, C_6H_5)
6	191–193 (EtOH)	67[c]	3400–3100 (OH), 1710,[h] 1650[g]	2.29 (s, 3H, CCH_3), 3.87 (s, 3H, NCH_3), 7.32–7.48 (m, 5H, C_6H_5)
7	195 (dec) (EtOH)	87[d]	3300–3100 (OH), 1640[g]	1.90 (s, 3H, $COCH_3$), 3.77 (s, 3H, NCH_3), 7.30–7.50 (m, 5H, C_6H_5), 11.10 (br s, 1H, NOH)
8	164–166 (dec) (EtOH)	75[e]	1670[g]	2.77 (s, 3H, CH_3C), 4.01 (s, 3H, NCH_3), 7.40–7.60 (m, 3H_{arom}), 8.20–8.35 (m, 2H_{arom})
11	191–193 (EtOH)	23[f]	3420, 3320 (NH_2), 1670[g]	1.70 (s, 3H, CH_3C), 3.78 (s, 3H, NCH_3), 7.45 (s, 5H, C_6H_5), 7.80 (br, 2H, NH_2)

[a] Satisfactory microanalyses obtained C ± 0.33, H ± 0.27, N ± 0.29.
[b] Compounds **7** and **11** were measured in DMSO-d_6.
[c] Based on starting nitro ketone **2**.
[d] Based on **6**.
[e] Based on **7**.
[f] Based on actually converted **2**.
[g] Amide carbonyl.
[h] Keto carbonyl.

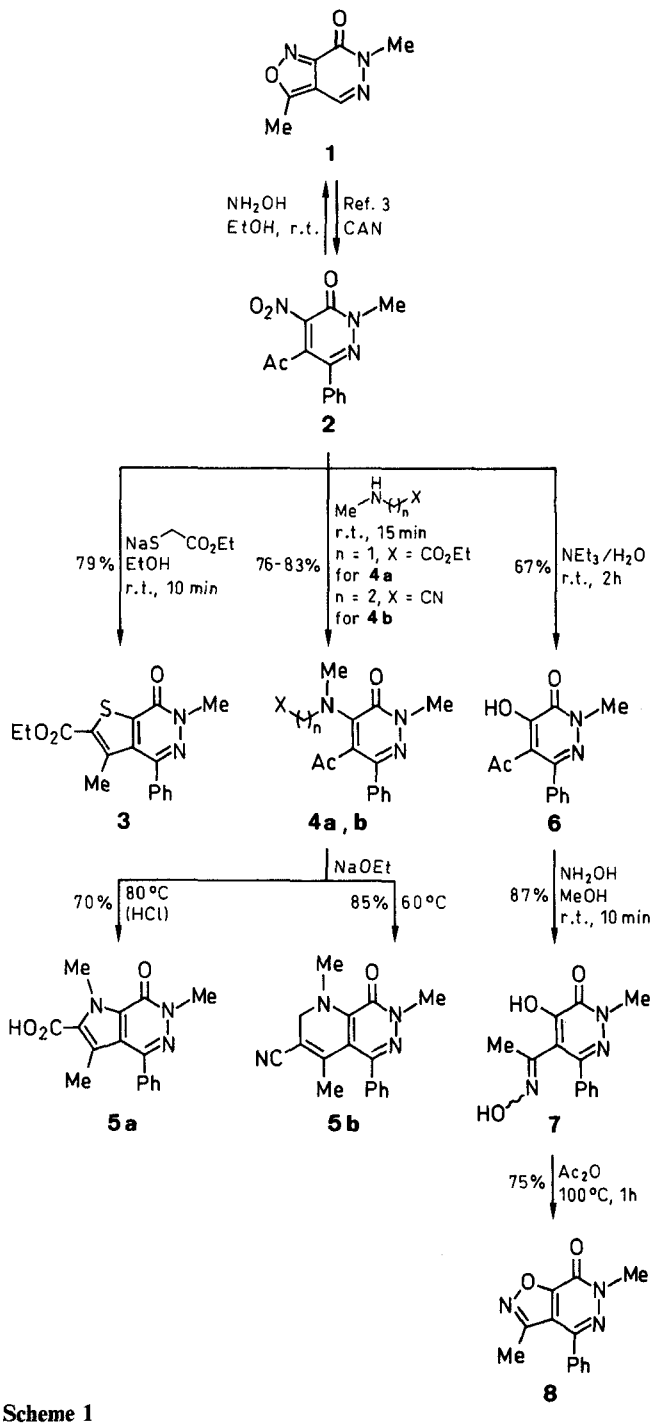
the ^{1}H NMR spectrum of **5a** ($\delta = 4.55$), and the signals for similar *N*-methyl five-membered-condensed pyridazinones, like 1-methyl-1*H*-pyrazolo[3,4-*d*]pyridazinones ($\delta = 4.32-4.33$), appear notably shifted downfield[8] (Table).

The isoxazolo[4,5-*d*]pyridazine derivative **8** was obtained, in a three-step procedure, starting from the same precursor **2** through the 4-hydroxypyridazinone **6** and the corresponding oxime **7**. It is noteworthy that the isolation of the intermediates **6** and **7** is unnecessary: compound **8** can also be prepared in a single one-pot procedure starting from **2** in 46% yield. On the other hand, it is impossible to obtain **8** by treatment of **2** with hydroxylamine because this reagent, both as free base and as hydrochloride, attacks preferentially the pyridazine 4-carbon rather than the carbonyl carbon in alcoholic medium. Thus the isomeric isoxazolo[3,4-*d*]pyridazine derivative **1**, which represents the synthetic precursor of **2**, was obtained. Therefore the above reaction sequence allowed the conversion of the isoxazolo[3,4-*d*]pyridazine derivative **1** into the isomeric isoxazolo[4,5-*d*]pyridazine **8** through the key intermediate **2**.

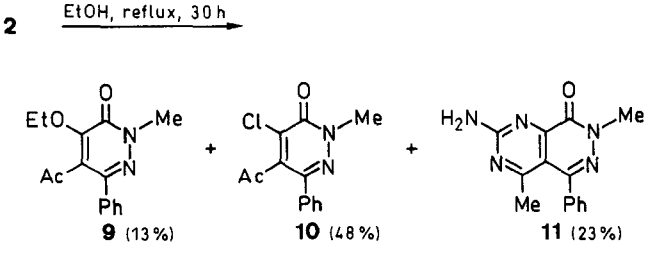
We encountered unexpected difficulties in the synthesis of pyrimido[4,5-*d*]pyridazinone **11** by cyclocondensation of **2** with guanidine as free base in a variety of solvents and experimental conditions. However, the desired product **11** was obtained in low yield (23%) by refluxing **2** with guanidine hydrochloride in ethanol for a long period of time (Scheme 2). From the reaction mixture we have recovered the starting material **2** (16%) by column chromatography, besides an unresolved fraction in which the 4-chloro derivative **10**[7] (48%) and the 4-ethoxypyridazinone **9**[12] (13%) were identified by their ^{1}H NMR data. Both the products clearly arise from a competitive nucleophilic displacement of the nitro group in **2** by the chlorine anion and by the solvent, respectively. Evidence for this hypothesis was obtained from the reaction between **2** and benzyltriethylammonium chloride (TEBA) in acetonitrile to form compound **10** in almost quantitative yield.

The IR and ^{1}H NMR data listed in the Table are in full agreement with the proposed structures. In particular the occurrence of the CO vibration at $\nu = 1640-1680\ cm^{-1}$ in the IR and the typical singlet observed at about $\delta = 3.80$ in the ^{1}H NMR spectra for the 2-methyl group of the pyridazinonic system confirm that in all the reaction products a cyclic lactamic structure is preserved. Moreover the singlets observed at about $\delta = 2.10$ for the CCH_3 groups in five-membered-condensed pyridazinones **3** and **5a** agree with the values found for structurally related compounds,[8] whereas the same signals appeared shifted highfield ($\delta = 1.64$ and 1.70) for the six-membered fused analogues **5b** and **11**.

In conclusion, the easy availability of the precursor **2** (obtained in 3 steps from commercial products) has made the present method an effective alternative synthetic approach to hetero-condensed pyridazinones by cyclocondensation[10] of suitable substituted heteroaromatics with hydrazine.



Scheme 1



Scheme 2

Melting points were determined on a Büchi 510 melting points apparatus and are uncorrected. IR spectra were measured as nujol mulls with a Perkin-Elmer 681 spectrometer. ^{1}H NMR spectra were recorded with Varian Gemini 200 instrument; Chemical shifts are reported in ppm, using the solvent as internal standard. Extracts were dried over Na_2SO_4 and solvents were removed under reduced pressure. Silica gel plates (Merck F254) were used for analytical TLC and silica gel (Merck 70–230 mesh) for column chromatography.

Ethyl 6,7-Dihydro-3,6-dimethyl-7-oxo-4-phenylthieno[2,3-*d*]pyridazine-2-carboxylate (3):
To a solution of sodium ethyl thioglycolate, prepared from NaOEt (170 mg, 2.5 mmol) and ethyl thioglycolate (300 mg, 2.5 mmol) in absolute EtOH (5 mL), was added compound **2** (110 mg, 0.4 mmol) at r.t. The mixture was stirred for 10 min, cooled at 0 °C and filtered. The residue, after washing with H_2O, was purified by recrystallization from EtOH to give colorless crystals (Table).

4-Disubstituted Amino-5-acetyl-2-methyl-6-phenyl-3(2*H*)-pyridazinones 4a,b; General Procedure:
A mixture of **2** (110 mg, 0.4 mmol) and the appropriate reagent (sarcosine ethyl ester, 70 mg, 0.6 mmol for **4a** or *N*-methyl β-alaninenitrile, 60 mg, 0.7 mmol for **4b**) in EtOH (3 mL) was stirred at r.t. for 15–30 min. The suspension was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). Evaporation of the solvent afforded the desired products which were purified by recrystallization to give colorless crystals of **4a** and **4b** (Table).

Ring Closure of 4a,b; General Procedure:
To a solution of NaOEt [from Na (55 mg, 2.4 mmol) and absolute EtOH (4 mL)] was added **4a** or **4b** (0.3 mmol) and the mixture was heated at 60–80 °C for 30 and 60 min, respectively. After evaporation of the solvent, **5a** was extracted with 5% aq $NaHCO_3$ filtered and precipitated with 2N HCl. The product was purified by recrystallization to give colorless crystals.

Compound **5b** was obtained as yellow crystals after precipitation with H_2O (30 mL), filtration and recrystallization (Table).

6,7-Dihydro-1,3,6-trimethyl-7-oxo-4-phenyl-1*H*-pyrrolo[2,3-*d*]pyridazine-2-carboxylic Acid (5a) and 1,2,7,8-Tetrahydro-3-cyano-1,4,7-trimethyl-7-oxo-5-phenylpyrido[2,3-*d*]pyridazine (5b); General Procedure for One-Pot Synthesis:
After treatment of **2** (110 mg, 0.4 mmol) with the appropriate reagent (0.6 mmol), as described above, a solution of NaOEt (200 mg, 2.9 mmol) in absolute EtOH (4 mL) was added and the mixture heated at 80 °C for 1 h. After evaporation of the solvent in vacuo, compounds **5a, b** were isolated as above (Table).

5-Acetyl-4-hydroxy-2-methyl-6-phenyl-3(2*H*)-pyridazinone (6):
To a stirred solution of **2** (200 mg, 0.73 mL) in MeCN (2 mL) and H_2O (0.2 mL) was added dropwise NEt_3 (1 mL) at r.t. After 2 h the mixture was evaporated in vacuo, and the residue treated with EtOAc (30 mL) and extracted with 1N NaOH (3 × 10 mL). The combined aqueous layers were acidified with 3N HCl to afford compound **6** which was purified by recrystallization to give colorless crystals (Table).

5-Acetoxyhydroximoyl-4-hydroxy-2-methyl-6-phenyl-3(2*H*)-pyridazinone (7):
To a solution of NH_2OH prepared from $NH_2OH \cdot HCl$ (500 mg, 17.2 mmol) in H_2O (1 mL) and NaOMe (390 mg, 7.2 mmol) in MeOH (4 mL) was added compound **6** (100 mg, 0.41 mmol) and the mixture stirred at r.t. for 15 min. After evaporation in vacuo, the residue was treated with H_2O (7 mL) to afford **7** which was purified by recrystallization to give colorless crystals (Table).

3,6-Dimethyl-4-phenylisoxazolo[4,5-*d*]pyridazin-7(6*H*)-one (8):
The oxime **7** (140 mg, 5.4 mmol) was heated with Ac_2O (2 mL) at 100 °C for 1 h under stirring. After cooling the solution was stirred with brine (15 g) for 30 min. The solid obtained was purified by recrystallization from EtOH to give colorless crystals (Table).

2-Amino-4,7-dimethyl-5-phenylpyrimido[4,5-*d*]pyridazin-8(7*H*)-one (11):
A suspension of **2** (200 mg, 0.73 mmol) and guanidine hydrochloride (900 mg, 9.4 mmol) in EtOH (7 mL) was stirred at reflux under N_2 for 35 h. After concentration in vacuo, the excess of guanidine hydrochloride was removed by filtration and the solution was further concentrated and chromatographed on silica gel (eluent: cyclohexane/EtOAc, 1:1). The starting material was recovered in the first fraction; then an unresolved mixture of **9** and **10** was collected. Compound **11** was obtained from the last fraction and purified by crystallization from EtOH to give colorless crystals (Table).

5-Acetyl-4-chloro-2-methyl-6-phenylpyridazin-3(2*H*)-one[7] (10):
A mixture of **2** (55 mg, 0.2 mmol) and TEBA (114 mg, 0.5 mmol) in MeCN (3 mL) was refluxed for 1 h. Evaporation of the solvent afforded a residue which was treated with H_2O (3 mL) and filtered. The product was identified as **10** by comparison of its IR and ^{1}H NMR spectra with those of an authentic specimen.[7]

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