# EFFICIENT AND FACILE SYNTHESES OF [4,5]-ANNELATED PYRIDAZINES FROM 4-PYRIDAZINECARBALDEHYDES

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***Abstract*** - New synthetic approaches to novel [4,5]-annelated pyridazine derivatives through the closely related intermediates, are described. These include derivatives of two angularly oriented ring systems (**4**) and (**5**), as well as those of pyrano[2,3-*d*]- and pyrazolo[3,4-*d*]pyridazines (**6**) and (**8**). The tertiary amino effect was successfully applied to the construction of the former compounds, whereas the latter compounds were formed by the cyclization based on addition-elimination sequences.

We recently described several novel series of 3(2*H*)-pyridazinones possessing characteristic pharmacological activities.[2] For structure-activity studies, [4,5]-or [*d*]-annelated bi- and tricyclic pyridazine derivatives have also been prepared as ring homologues, or as promising pharmacophors *per se*. These include pyridazino-oxazines, -oxazepines, their thia analogues,[3] and phthalazines.[4] As an extension of these series of studies, we describe here the synthesis of two new pyridazine heterocyclic analogues, containing pyrido[2,3-*d*]pyridazine skeleton, as well as the preparations of pyrano[2,3-*d*]- and pyrazolo[3,4-*d*]pyridazines in simple and efficient ways. Principally, two synthetic strategies for construction of these compounds are feasible, i) elaboration of the pyridazine moiety on the other heteroring, or ii) constructing the heteroring on the pyridazine. In fact, pyrido[2,3-*d*]pyridazines[5,6] and pyrazolo[3,4-*d*]pyridazines[7,8] have already been synthesized in both pathways, whereas the latter route has been preferred for pyrano[2,3-*d*]pyridazines.[9]

We focused on the possible usage of the same or closely related intermediates in order to open general and widely applicable ways to a variety of [4,5]-fused pyridazine systems. The tertiary amino effect[10] was considered as a particularly efficient methodology for preparation of angularly annelated ring systems. For this purpose, 5-substituted 4-pyridazinecarbaldehydes (**2**) were prepared and used as key intermediates. Thus, the

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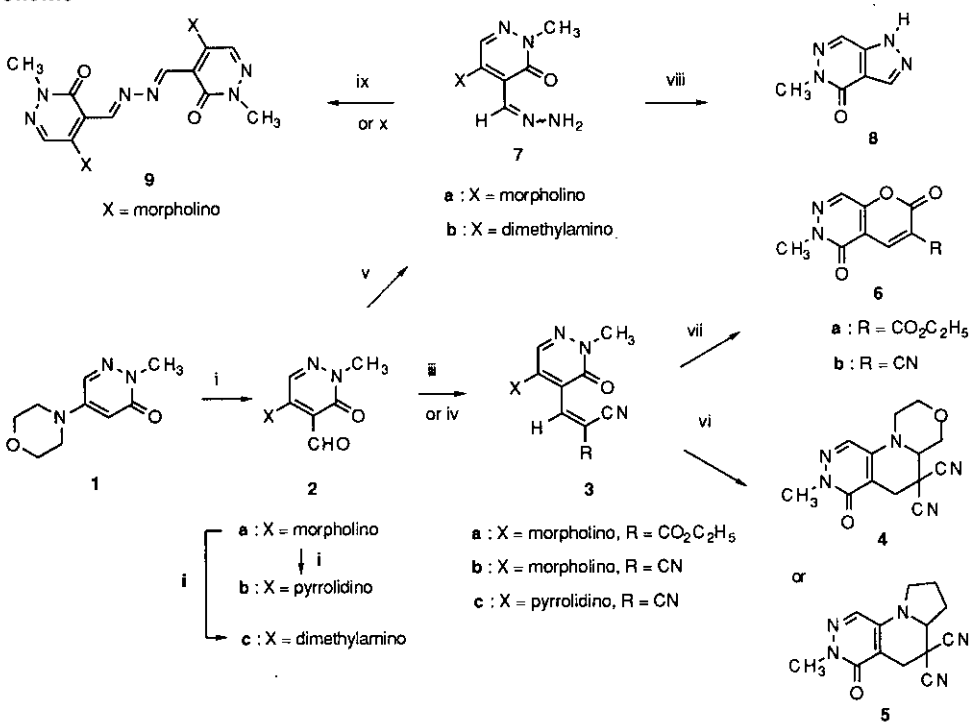
This article is dedicated to Professor Alan R. Katritzky on his sixty-fifth birthday.

Vilsmeier-Haack formylation of 2-methyl-5-morpholino-3(2*H*)-pyridazinone (**1**)[11] afforded **2a** in high yield. The related formyl derivatives (**2b**) and (**2c**) were easily obtained from **2a** by using appropriate secondary amines as nucleophiles (Scheme). Condensation of **2a,b** with ethyl α-cyanoacetate or malononitrile in ethanol under conditions described in Scheme, provided **3a-c** in a fairly good yield.[13] The *E*-isomer (**3a**) was predominantly formed in a ratio of 44 : 1 as proved by its nmr spectra, which indicated vinylic protons at δ 8.13 for the *E*-isomer and 7.66 for the *Z*-isomer. Additionally, the values of coupling constants between the ester carbonyl, nitrile carbon and the vinylic hydrogen in the $^{13}C$ nmr spectrum (*J* (CO,H) 3.7 and *J*(CN,H) 13.9 Hz) confirmed the *E*-geometry.

**Scheme**[a]




[a]Reagents and conditions : i) $POCl_3$ - DMF, 70 °C, 1 h; ii) $R_2NH$ (excess), room temperature, 1 d; iii) $CNCH_2CO_2C_2H_5$, $C_2H_5OH$-pyrrolidine-AcOH, room temperature, 1 d for **3a**; iv) $(CN)_2CH_2$, $C_2H_5OH$, room temperature, 3 d, for **3b** and **3c**; v) $N_2H_4 \cdot H_2O$, $C_2H_5OH$, room temperature; vi) **3b,c**, DMSO, 150 °C, 44 h for **4** and 39 h for **5**; vii) 2 ~ 4*N* HCl, room temperature, 4h; viii) $N_2H_4 \cdot H_2O$ (20 eq.), $C_2H_5OH$, 80 °C, 20 h; ix) **7a**, AcOH, room temperature ~ 80 °C; x) **7a**, **2a**, $C_2H_5OH$, room temperature, 1 d.

Compound (**3b**) did not cyclize in boiling *n*-butyl acetate for long period of time, but the reaction took place in DMSO at 150 °C to give **4** in 35 % yield. In the same way, cyclization of **3c** provided **5** in 44 % yield. Compounds (**4**) and (**5**) are the first representatives of the pyridazino[4,5:5,6]pyrido[2,1-*c*][1,4]oxazine and

pyrrolo[2,1:6,1]pyrido[2,3-*d*]pyridazine ring systems, respectively. These structures were easily deduced from their nmr spectroscopic data, in which the methylene protons vicinal to the carbons bearing cyano groups for **4** and **5** appeared as *AB* quartet at δ 3.10, 3.63 with $J$ = 18.0 Hz and 2.97, 3.80 ppm with $J$ = 17.6 Hz, respectively. The bridgehead carbons of C-4a and C-3a (δ 66.0 and 62.3 ppm) were also of diagnostic importance. In contrast, the ester analogue (**3a**) was unreactive under similar conditions, and prolonged heating of the reaction mixture resulted in formation of a complex mixture, from which none of the cyclized products were isolated. These results suggest that the reaction is significantly dependent on the induced effect of the substituent.

Next, we turned our attention to the synthesis of pyrano[2,3-*d*]pyridazine system. Although elegant preparations of 3-alkyl- and 3-aryl-2,5-dioxo derivatives were reported,[9] analogues with electron-withdrawing substituent at the 3-position have not yet been described. An extremely simple and efficient route was developed for the preparation of such compounds. Thus, both the ester and nitrile derivatives (**3a,b**) was transformed into **6a** and **6b** by treatment with diluted aqueous hydrogen chloride at room temperature. The infrared spectroscopic data ($\nu_{KBr}$ 1785, 1700, and 1650 for **6a**; 2350, 1770, and 1650 $cm^{-1}$ for **6b**) support these structures. The following steps might be involved in these reactions, i) the nucleophilic displacement of the morpholino group by OH group, or acidic hydrolysis of the nitrile group, ii) intramolecular (imino)lactonization[14] and iii) hydrolysis of the *in situ* formed imino group to carbonyl.

Finally, we investigated the preparation of pyrazolo[3,4-*d*]pyridazine ring system possessing no substituent at the $N_1$ position. The aldehyde (**2a**) was readily condensed with $N_2H_4 \cdot H_2O$ to afford the hydrazone (**7a**), which was expected to cyclize to **8**. Attempted cyclization in acetic acid[15] gave, however, complex mixture, from which the 'dimer' (**9**) was isolated in a 20 % yield. On the other hand, the cyclization was achieved to yield **8** (δ 8.35 ppm for CH-3,7, and δ 117.2, 130.5, 134.6, 143.5, 161.0 ppm for ring carbons; $\nu_{KBr}$ 3420, 1660 $cm^{-1}$) by treatment of **7a** with excess of $N_2H_4 \cdot H_2O$ in boiling ethanol. Furthermore, the better yield of **8** was obtained with **7b** suggesting the better leaving group character of the dimethylamino group under these conditions.

In conclusion, we reported here the straightforward synthesis of new [4,5]-fused pyridazines based on the tertiary amino effect annelation principle and using addition-elimination sequences. Further work is now in progress to evaluate the biological activity of the sythesized compounds and sythetic potential to the other type of the fused heterocycles.

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