A New Route for the Synthesis of Pyrido[2,3-*d*]pyridazines

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A new simple route for the synthesis of pyrido[2,3-*d*]pyridazines by reaction of acetyl and benzoyl cyanides with α,β-unsaturated nitriles is reported.

Although pronounced diuretic and antihypertensive activity have been demonstrated for pyrido[2,3-*d*]pyridazines,[1,2] most of their synthesis from both pyridine and pyridazine intermediates are multistageous and afford only poor yields of end products.[3,4]

In connection with our interest in the synthesis and biological evaluation of condensed azines,[5,6] we report here a new, efficient and simple route for the synthesis of pyrido[2,3-*d*] pyridazines. Thus, it is found that acetyl cyanide (**1a**)[7] and benzoyl cyanide (**1b**)[7] react with 1,1,3-tricyano-2-amino-1-propene (**2a**)[8] to yield the acylpyridines **4a** and **4b**, respectively. Structure **4** is preferred over possible **3** based on ^{1}H-NMR spectroscopy, which reveals the absence of signal for CH_2CN as expected for pyridine **4**. The formation of **4** from the reaction of **1a** and **1b** with **2a** is assumed to proceed via addition of the active methylene moiety in **2a** and subsequent cyclization. Compound **2b**[9] also reacts with **1a** and **1b** to yield product of condensation via ethanol elimination and for which structures **4c** and **4d**, respectively, is suggested.

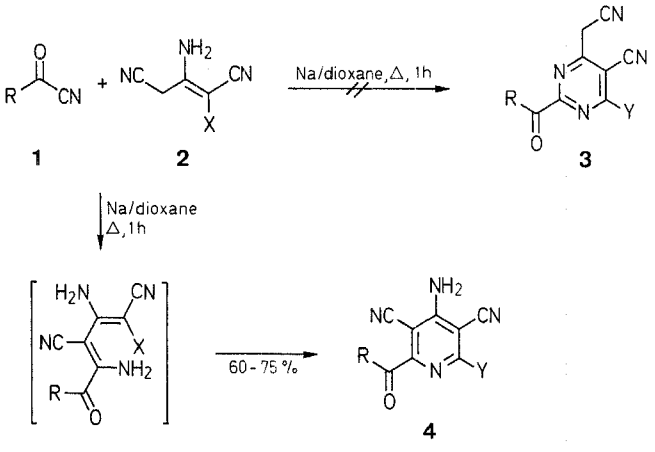
Compounds **4a** and **4b** react with hydrazine hydrate to yield the pyrido[2,3-*d*]pyridazines **6a** and **6b**, respectively, and not the acyclic **5** and indicated from infra red spectra, which reveal only one peak for the cyano group.

Similarly, the pyrido[2,3-*d*]pyridazines **6c** and **6d** are obtained via the reaction of **4c** and **4d**, respectively, with hydrazine hydrate. Compounds **6b** and **6d** showed M + 1 ion peak in their mass spectra. Such behavior has been observed previously for polyamino compounds.[10]

Table. Compounds **4** and **6** Prepared

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a]	IR (KBr) ν (cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS) δ	MS *m/z*
4a	75	173 (EtOH)	$C_9H_7ON_5$ (201.2)	3450, 3220 (NH_2); 2910 (CH_3); 2210, 2200 (CN)	3.2 (s, 2H, NH_2); 3.4 (s, 3H, CH_3); 7.8 (br, 2H, NH_2)	201
4b	72	245 (EtOH)	$C_{14}H_9ON_5$ (263.3)	3350, 3200 (NH_2); 2200, 2190 (CN); 1700 (CO)	5.2 (s, 2H, NH_2); 6.9–7.6 (m, 5H, C_6H_5); 7.9 (s, 2H, NH_2)	263
4c	65	212 (EtOH)	$C_9H_6O_2N_4$ (202.2)	3350, 3100 (NH_2); 2200, 2190 (CN)	3.5 (s, 3H, CH_3); 5.2 (s, 2H, NH_2)	202
4d	60	154 (EtOH/H_2O)	$C_{14}H_8O_2N_4$ (264.3)	3400, 3100 (OH and NH_2); 2200, 2190 (CN)		264
6a	65	250 (EtOH/H_2O)	$C_9H_9N_7$ (215.2)	3350–3100 (br, NH_2); 2200 (CN)	2.8 (s, 3H, CH_3); 5.2 (s, 2H, NH_2); 7.8–8.2 (br, 4H, $2NH_2$)	215
6b	65	222 (EtOH/H_2O)	$C_{14}H_{11}N_7$ (277.3)	3350–3100 (br, NH_2); 2200 (CN)	5.3 (s, 2H, NH_2); 6.9–7.6 (m, 5H, C_6H_5); 9.7–8.3 (br, 4H, $2NH_2$)	278
6c	65	250 (EtOH)	$C_9H_8ON_6$ (216.2)	3450–3100 (OH and NH_2); 2200 (CN)	–[b]	
6d	60	228 (DMF/H_2O)	$C_{14}H_{10}ON_6$ (278.3)	3450–3100 (OH and NH_2); 2200 (CN)	5.7 (s, 2H, NH_2); 7.0–7.8 (m, 5H, C_6H_5); 8.0 (s, 2H, NH_2)	279

[a] Satisfactory microanalyses obtained: C ±0.3, H ±0.2, N ±0.3.
[b] No ^{1}H-NMR spectrum could be taken due to its insolubility in common solvents used for spectral measurement.



1,2	R	X
a	CH_3	CN
b	C_6H_5	$CO_2C_2H_5$

All melting points are uncorrected. IR spectra were recorded on a Shimadzu 408 spectrometer and ^{1}H-NMR spectra were measured on a Varian EM-390-90 MHz spectrometer. Mass spectra were obtained by electron impact method. The microanalyses were performed by the microanalytical unit at Cairo University.

2,6-Disubstituted 4-Amino-3,5-dicyanopyridine Derivatives 4a–d; General Procedure:

A mixture of the acylcyanide **1a** or **1b** (0.01 mol) and the appropriate **2a** or **2b** (0.01 mol) is heated under reflux in dioxane (50 mL) in the presence of catalytic amount of sodium (0.1 g) for 1 h. The mixture is then evaporated *in vacuo* and neutralized with conc. HCl. The solid product, so formed, is collected by filtration and recrystallized (Table).

2,8-Disubstituted 4,5-Diamino-3-cyanopyrido[2,3-*d*]pyridazine Derivatives 6a–d; General Procedure:

The appropriate compound **4a–d** (0.01 mol) is heated with hydrazine hydrate (0.6 g; 0.012 mol) at 100 °C for 4 h. The product formed is triturated with water, collected by filtration and recrystallized (Table).

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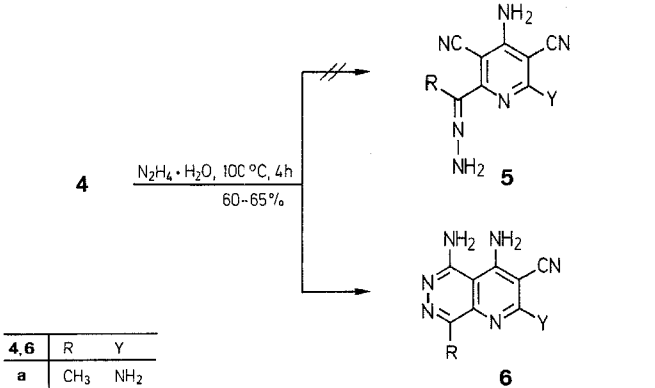

4,6	R	Y
a	CH_3	NH_2
b	C_6H_5	NH_2
c	CH_3	OH
d	C_6H_5	OH

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