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Heterocyclic synthesis with nitriles: Synthesis of pyridazine and pyridopyridazine derivatives.

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The reaction of MND with aryl diazonium chlorides followed by cyclization afforded the pyridazinimine derivatives. Reaction of the latter with another mole of malononitrile produce only pyrido[3,2-*c*]pyridazine derivatives. Reaction of 4-aminopyridazinone-3-carboxylic acid esters with malononitrile gave only pyridazine-3-carboxylic acid.

Introduction

During the past few decades increasing interest in the synthesis and properties of pyridazines, pyridazinones, pyridopyridazines, and pyridopyridazinones has been observed.

Pyridopyridazines and pyridopyridazinones show wide spectrum of biological activities as described in the literature [1-4]. Both classes of substances are of interest as antiviral and cancer therapies, since their structures and properties resemble those of certain current pteridines and purines.

Recently the pyridazinone nucleus has been extensively studied in the search for new and selective medicinal agents as drugs acting on the cardiovascular system [5,6]. It has been discovered that several aminopyridazinones showed remarkable biological activities; for example, nootropic (memory-improving) [7].

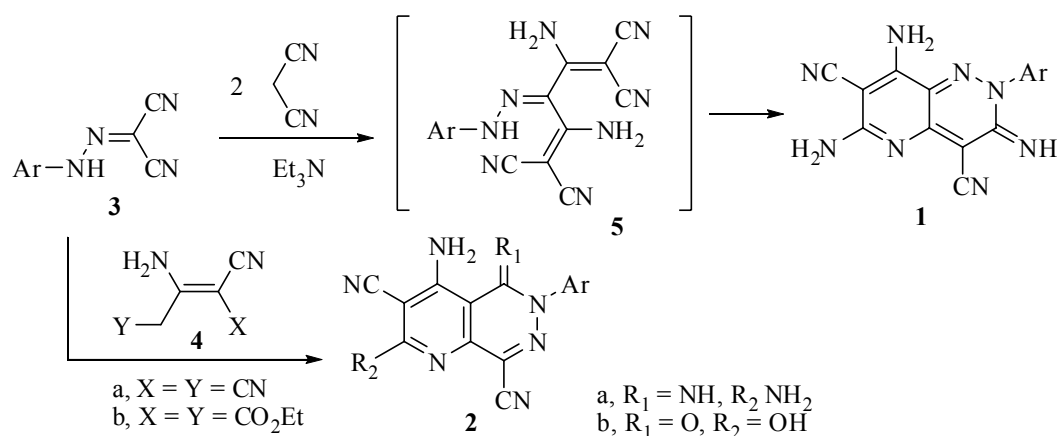
In contrast to the phthalazinones, their aza analogs, pyridopyridazinones, are as yet relatively little studied. The primary reasons for this are the difficulties associated with the preparation of pyridine starting materials which can easily be transformed into pyridopyridazinones. The only general method for the synthesis of that system involves the cyclization of *o*-acylpyridinecarboxylic acids [8] and their derivatives (ester [8] and disubstituted amides [9] or of methyl esters of *o*-cyanopyridinecarboxylic acids [10] with hydrazine and monosubstituted hydrazines).

Continuing our interest on the synthesis of pyridazinones [11,12] we hereby present results using a method which was previously employed in only a few cases to the preparation of pyridazinones [13].

Results and Discussion

The literature showed that—compounds **1** and **2** could be obtained from cyclocondensation of arylhydrazonomalononitriles with malononitrile, 2-amino-1,1,3-tricyanopropene, and 3-amino-2-cyanopent-2-ene dicarboxylate [14], [15] respectively (Scheme 1).

It was decided to build compounds of type **1** and **2** by both routes, from the reaction of 3-methoxyphenylhydrazonomalononitrile with two equivalents of malononitrile (MN) and from coupling of arene diazonium chloride with 2-amino-1,1,3-tricyanopropene (MND), and 3-amino-2-cyanopent-2-ene dicarboxylate (ethyl or methyl cyano dimmer) to obtain pyridazine derivatives and further reaction of the latter with another mole of MN to obtain the desired products and confirm the way of cyclization of those compounds when reacted with MN.



Scheme 1

The reaction of compound **4a** (MND), with aryldiazonium chlorides followed by cyclization in ethanolic triethylamine afforded the pyridazinimine derivatives **8a,b**. Reaction of compounds **8a,b** with another mole of malononitrile could take place in two different pathways to afford pyrido[3,2-*c*]pyridazine or pyrido[2,3-*d*]pyridazine derivatives.

It was found that the reaction of pyridazine derivatives **8a,b** with malononitrile afforded **1a,b** in a good yield. Compounds **1a,b** could also be obtained from the reaction of **7a,b** with malononitrile under refluxing in ethanolic triethylamine solution for 4 h. The data in our hands, IR, mass, ¹H and ¹³C NMR, are in accordance with the structure of pyrido[3,2-*c*] pyridazines **1** [15, cf. experimental part] (Scheme 2).

Moreover, the presence of a significant NOE enhancement between the NH group and CH aromatic protons in structure **1** and the absence of NOE between NH and NH₂ group for structure **2** allowed establishing the structure **1**. Using Chemdraw 3D Pro, the distance between the imino H and the closest aromatic protons is 1.2072 Å, which supports the 7.9% enhancement observed.

The reaction of 2-(1-amino-2-cyanoethylidene)malonic acid diethyl **4b** or dimethyl **4c** ester and 4-chlorobenzene diazonium chloride –afforded the hydrazo derivative **11a,b** which could be cyclised into pyridazinones **12a,b**. The reaction of compounds **12a,b** with malononitrile produced only pyridazine-3-carboxylic acid **13** which could also be obtained by boiling of compound **11** in ethanolic triethylamine solution for a long time (Scheme 2).

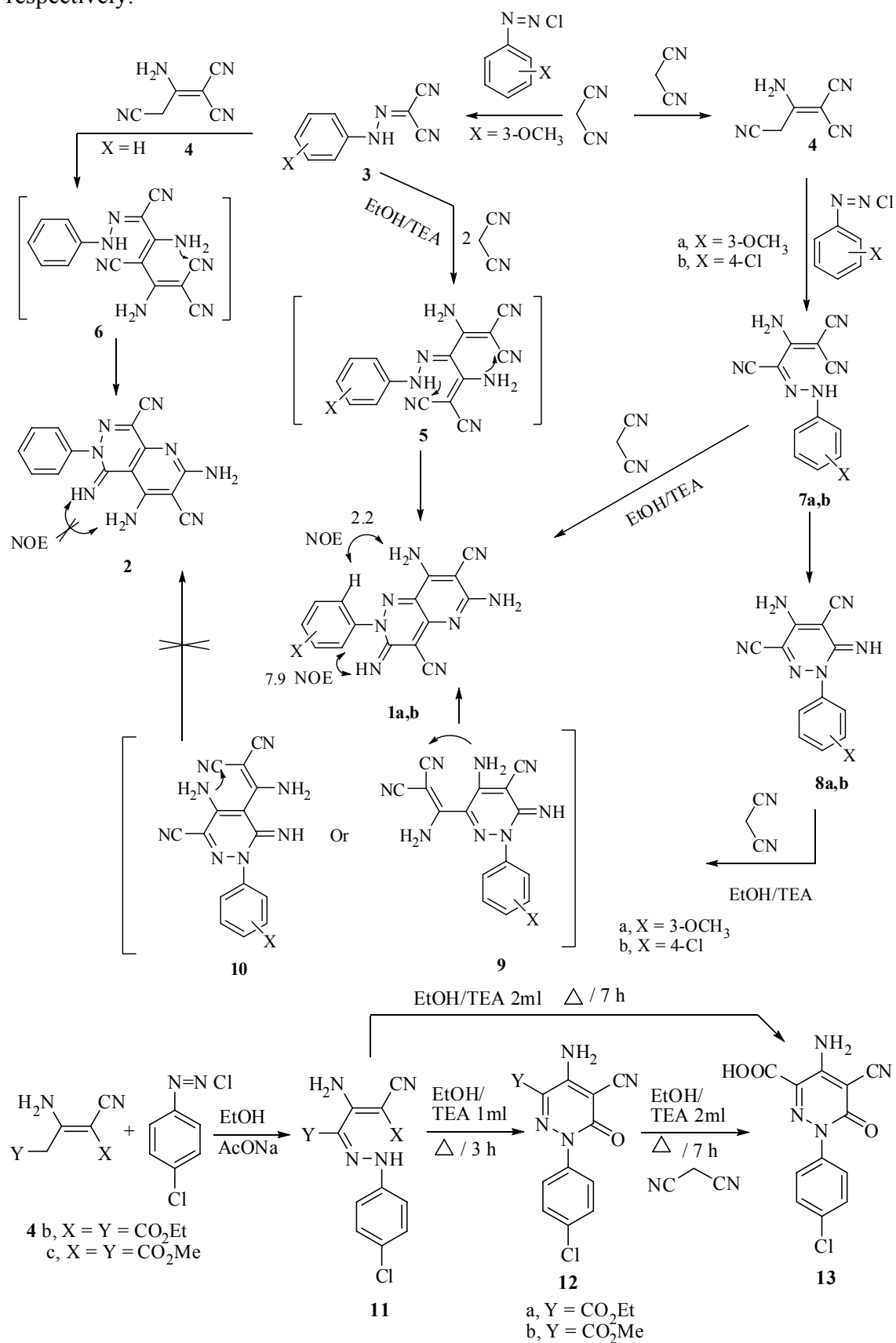
Experimental

All melting points were measured on a Gallenkamp apparatus and are uncorrected. IR spectra were determined on a Perkin Elmer FTIR-1600 using Nujol emulsions between NaCl plates. ¹H NMR spectra were recorded at 300 MHz and ¹³C NMR spectra were determined at 75.4 MHz both on Varian Unity plus spectrometer. In the NMR spectra TMS was used as internal reference. Low resolution EI mass spectra were determined on a Unicam GC-MS 120. FAB or high resolution mass spectra were obtained on a VG Ultima or AutoSpec E spectrometers. Elemental analysis data were obtained on a Leco CHNS-932.

General procedure for the preparation of compounds **8a,b** and **12a,b**

To a solution of each of **7a,b** and **11a,b** (10 mmol) in ethanol (25 ml) was added triethylamine (1ml). The reaction mixture was refluxed for 2-6 h, then allowed to cool,

the precipitated solid products formed were collected by filtration, washed with cold water, and recrystallized from ethanol or ethanol/DMF (1:1) to afford **8a,b** and **13a,b** respectively.



Scheme 2

4-Amino-6-imino-1-(3-methoxyphenyl)-1,6-dihydro-pyridazine-3,5-dicarbonitrile (8a). Red powder, Yield 92 %, mp > 300°C ethanol/DMF (1:1), ¹H NMR (300 MHz, DMSO-d₆) δ, 3.77 (s, 3H, CH₃), 7.04-7.08 (m, 3H, Ar-H), 7.41-(s, 1H, NH), 7.43 (s, 1H, Ar-H), 7.48 (br, 2H, NH₂). Anal. Calcd. for (C₁₃H₁₀N₆O): C, 58.64; H, 3.79; N, 31.56. Found C, 58.51, H, 4.01, N, 30.99.

4-Amino-1-(4-chlorophenyl)-6-imino-1,6-dihydro-pyridazine-3,5-dicarbonitrile (8b). Red powder, Yield 90 %, mp > 300°C [Lit. mp mp > 300°C 16], ethanol/DMF (1:1), ¹H NMR (300 MHz, DMSO-d₆) δ, 6.82 (s, 1H, NH), 7.7 (d, 2H, *J* = 9 Hz, Ar-H), 7.99 (d, 2H, *J* = 9 Hz, Ar-H), 8.68 (s, 2H, NH₂).

4-Amino-1-(4-chloro-phenyl)-5-cyano-6-oxo-1,6-dihydro-pyridazine-3-carboxylic acid ethyl ester (12a). Yellow powder, Yield 92 %, mp 290-292°C ethanol/DMF (1:1), MS (EI), *m/z* = 318 [*M*⁺, 24.8 %], 320 [(*M*+2)⁺, 5 %]. ¹H NMR (300 MHz, DMSO-d₆) δ, 1.26 (t, 3H, *J* = 7Hz, CH₃), 4.33 (q, 2H, *J* = 7Hz, CH₂), 7.51-7.60 (m, 4H, Ar-H), 8.20 (brs, 2H, NH₂).

4-Amino-1-(4-chloro-phenyl)-5-cyano-6-oxo-1,6-dihydro-pyridazine-3-carboxylic acid methyl ester (12b). Yellow powder, Yield 80 %, mp 279-280°C ethanol/DMF (1:1). ¹H NMR (300 MHz, DMSO-d₆) δ, 3.83 (s, 3H, CH₃), 7.51-7.60 (m, 4H, Ar-H), 8.10 (s, 1H, NH), 8.42 (s, 1H, NH). Anal. Calcd. for (C₁₃H₉ClN₄O₃): C, 51.25; H, 2.98; N, 18.39. Found C, 51.24; H, 3.03; N, 18.39.

General procedure for preparation of compounds 1a,b

To a solution of each of **7a,b** and **8a,b** (10 mmol), malononitrile (10 mmol) in ethanol (25 ml) was added triethylamine (1ml). The reaction mixture was refluxed for 3 h, then allowed to cool, the precipitated solid products formed were collected by filtration, washed with ethanol, and recrystallized from ethanol/DMF (1:2) to afford **1a,b**.

6,8-Diamino-3-imino-2-(3-methoxyphenyl)-2,3-dihydropyrido[3,2-c]pyridazine-4,7-dicarbonitrile (1a) Red powder, Yield 94 %, mp > 300°C ethanol/DMF (1:1), (Lit. mp > 360°C, 15), IR, 2217 (CN), 3355, 3457(NH, NH₂). ¹H NMR (300 MHz, DMSO-d₆) δ, 3.79 (s, 3H, CH₃), 6.29 (brs, 1H, NH, exchangeable D₂O), 7.03 (dd, 1H, *J* = 9 Hz, 2.1 Hz, Ar-H), 7.15 (m, 2H, Ar-H), 7.43 (t, 1H, *J* = 9Hz, Ar- H), 7.63 (brs, 1H, NH, exchangeable D₂O), 8.08 (s, 2H, NH₂, exchangeable D₂O), 8.26 (brs, 1H, NH, exchangeable D₂O). ¹³C NMR (75.4 MHz, DMSO-d₆) δ 56.4 (CH₃), 70.9 (C-7), 89.8 (C-4), 112.4 (C-2'), 114.7 (CN), 114.8 (C-4'), 115.9 (CN), 118.5 (C-6'), 126.2 (C-9), 129.8 (C-5'), 141.8 (C-1'), 148.9 (C-9a), 154.3 (C-3), 155.4 (C-8), 159.7 (C-3'), 161.4 (C-6). MS (FAB) *m/z* 333 (*M*⁺ + 1, 100%). Anal. Calcd. for (C₁₆H₁₂N₈O): C, 57.83; H, 3.64; N, 33.72. Found C, 57.49, H, 4.02, N, 33.95.

6,8-Diamino-2-(4-chlorophenyl)-3-imino-2,3-dihydropyrido[3,2-c]pyridazine-4,7-dicarbonitrile (1b). Red powder, Yield 90 %, mp > 300°C ethanol/DMF (1:1), ¹H NMR (300 MHz, DMSO-d₆) δ, 6.50 (s, 1H, NH), 7.57 (d, 2H, *J* = 9 Hz, Ar-H), 7.68 (d, 2H, *J* = 9 Hz, Ar-H), 7.69(s, 1H, NH), 8.10 (s, 2H, NH₂), 7.69, 8.29 (s, 1H, NH).

4-Amino-1-(4-chlorophenyl)-5-cyano-6-oxo-1,6-dihydro-pyridazine-3-carboxylic acid 13. To a solution of each of **11a,b** and **12a,b** (10 mmol) in ethanol (25 ml) was added triethylamine (1ml). The reaction mixture was refluxed for 7 h, then allowed to cool, the precipitated solid product formed was collected by filtration, washed with ethanol, and recrystallized from ethanol/DMF (1:1) to afford **13**. Reddish brown powder, mp 244-246°C (EtOH), in 74% yield. ¹H NMR (300 MHz, DMSO-d₆) δ, 7.52 (m, 5H, 4Ar-H, 1H, NH), 8.16 (s, 1H, NH), 10.47 (s, 1H, COOH).

Acknowledgements

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