Synthesis of Pyridazine Derivatives through the Unexpected Intermediate 5-Amino- 4-Cyano -2,3-Dihydro-Furan-2,3-Disulfonic Acid Disodium Salt

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An unexpected compound (5-amino-4-cyano-2,3-dihydrofuran-2,3-disulfonic acid disodium salt, **4**) was isolated from the reaction of glyoxale bis hydrogen sulfite disodium salt with malononitrile. Its structure was undoubtly identified through crystal structure analysis. Compound **4** was highly stable and it was isolated easily and in a very high yield. Its reactivity was studied in the reactions with some hydrazine derivatives in order to obtain different pyridazine analogs.

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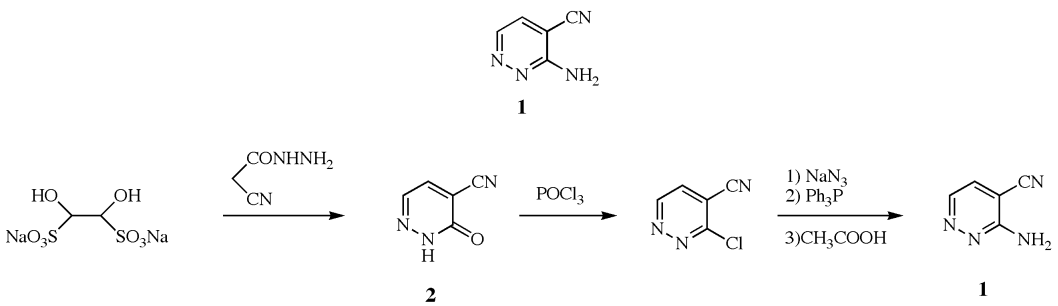
The pyridazine nucleus is a very common feature in many compounds of biological interest. Its employment gave good results in several fields of medicinal chemistry, such as PDE_4 inhibitors for inflammatory diseases [1], as endothelin-A receptor antagonists [2], in the development of active compounds toward α_1 and α_2 adrenoceptors [3], as central analgesics and aldose reductase inhibitors [4].

Due to this wide use of pyridazine based structures, great attention has been paid to the development of different methodologies for the preparation of pyridazine itself and its functionalized derivatives.

During a study on the synthesis of bicyclic heteroaromatic structures for a random screening program for searching new adenosine receptors antagonists, the pyridazine nucleus represented a classical bioisosteric substitution of phenyl ring which could confer a better water solubility or create possible hydrogen bonds with the receptor. In the literature, different functionalized pyridazine derivatives are reported; in particular, the 3-amino-4-cyano-pyridazine **1** was selected as ideal starting material for our purposes. Its preparation was reported starting from the hydrazide of ethyl cyanoacetate and glyoxale bis hydrogen sulfite disodium salt to furnish the 4-cyano-2*H*-pyridazin-3-one (**2**), followed by many steps to afford the desired amino nitrile derivative (Scheme 1) [4-8].

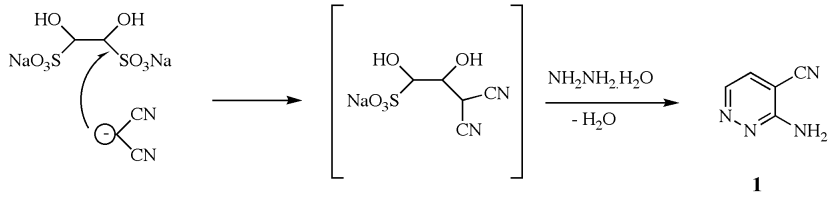
In order to obtain quickly and easily the desired pyridazine derivative, in analogy to the reported strategy, we tried to react the glyoxale bis hydrogen sulfite disodium salt, characterized by a more controlled reactivity with respect to the glyoxale itself, with malononitrile in an attempt to obtain a possible intermediate suitable for the reaction with hydrazine to afford compound **1** (Scheme 2)

Scheme 1



Synthesis of 3-amino-4-cyano-pyridazine reported in the literature

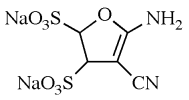
Scheme 2



Projected synthesis of 3-amino-4-cyano-pyridazine

This pathway was necessary because the simple reaction of glyoxale, malononitrile and hydrazine led to a complex mixture of different and unidentified products, as reported in the literature [6]. The other possibility to react the hydrazine with malononitrile as analog of the hydrazide of the ethyl cyanoacetate, was known to furnish 3-cyanomethyl-4-cyano-5-aminopyrazole (**3**) [9].

Surprisingly, the reaction of malononitrile with the glyoxale bis hydrogen sulfite disodium salt gave in a high yield a crystal intermediate (**4**), whose structure was characterized undoubtly by NMR and X-ray studies (Figure 1).



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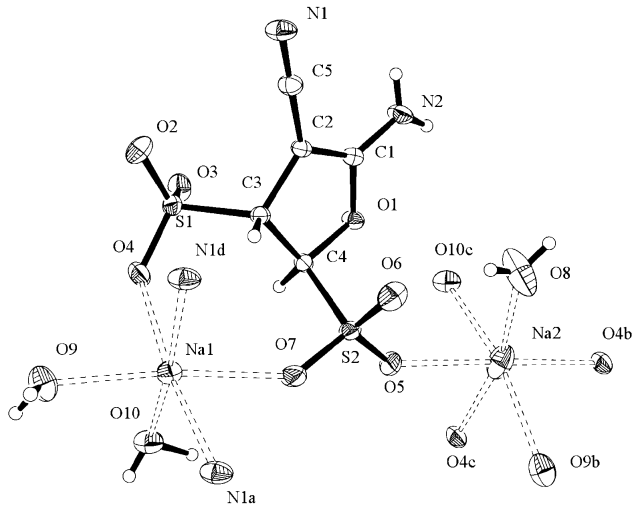


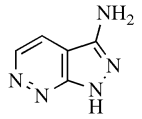
Figure 1. ORTEP [13] view of compound **4** displayng the thermal ellipsoids at 40% probability

Actually, the characterization through a crystal structure analysis of compound **4** was necessary due to the difficult interpretation of the simple ^{1}H NMR, performed in D_2O which showed just two doublet coupled signals.

The hypothesized reaction mechanism involved in the formation of this compound starts from the attack of the malononitrile anion, whose generation is derived by treatment with sodium hydroxide or sodium hydrogen carbonate, on the carbon of the glyoxale bis hydrogen sulfite. This step did not seem to induce sulfur group to leave as expected, but the elimination of the hydroxy group. Subsequently, an intramolecular cyclization of the second oxygen atom of the carbon of the glyoxale on the cyano group produced compound **4**, again without elimination of the sulfur group (Scheme 3).

The unexpected formation of this stable intermediate led us to investigate the reaction with hydrazine. The reaction of **4** with hydrazine monohydrate produced in a good yield the compound **5** (3-amino-1*H*-pyrazolo[3,4-*c*]pyridazine) through a possible presumed pathway reported in Scheme 4. This mechanism involves a double attack of the hydrazine with the opening of the ring, followed by a Michael addition to the α,β unsatured nitrile to form the pyridazine ring with water and ammonia elimination, and subsequent intramolecular cyclization on the cyano group to furnish the bicyclic final structure (**5**) (Figure 2).

Compound **5** has already been reported in the literature, but its synthesis was based on the reactivity of 2,5-dichloro-3-cyano-pyridazine, prepared through several steps [7,10]. This attractive reactivity of compound **4**,



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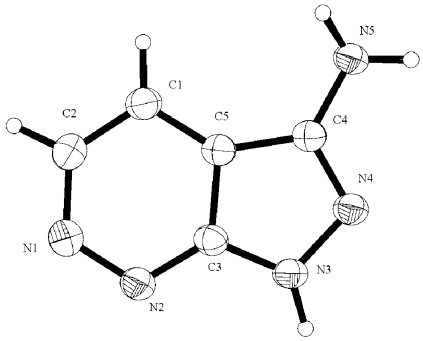
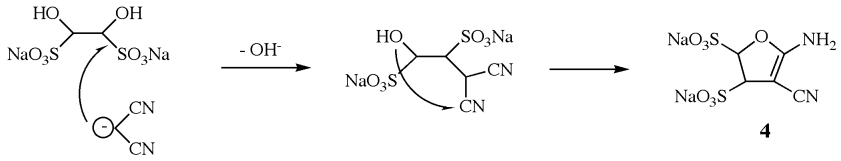


Figure 2. ORTEP [13] view of compound **5** displaying the thermal ellipsoids at 40% probability

Scheme 3



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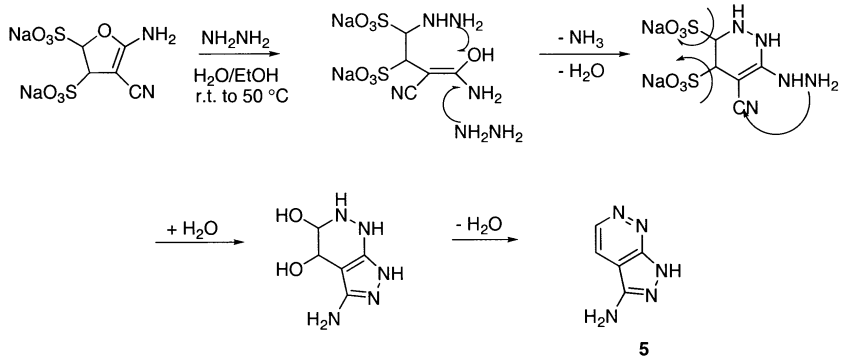
Proposed mechanism for the formation of compound **4**

Scheme 4



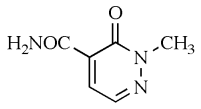
prompted us to investigate the reaction with a substituted hydrazine, such as methyl hydrazine, in order to verify if the sulfur groups were good leaving groups even in these conditions.

With methyl hydrazine the synthetic conditions utilized for unsubstituted hydrazine (Method A) gave comparable results, from a mechanistic point of view, but in a very low yield (27%), permitting recovery of the starting material. This different result could be attributed to the non-aromatic character of the final compound, which most probably could be considered the driving force of the process. Nevertheless, forcing the reaction conditions ($AcOH/H_2O$, reflux 24 hours, Method B) the yield was significantly increased from 27 to 78%. The simple pyridazine ring (**6**) so formed was easily hydrolized in the acqueous reaction enviroment (Scheme 5). Whereas the attempt with the phenyl hydrazine did not furnish any compounds in the same conditions, probably due to steric hindrance and lower nucleophilicity which hampered a similar pathway.

Compound **6** (2-methyl-3-oxo-pyridazine-4-carboxamide) was characterized by ^1H NMR and X-ray studies (Figure 3). The supposed mechanism shows the possible double attack by the less sterically hindered nitrogen of the hydrazine rather than the more basic one, with water elimination to give the pyridazine structure. Then, a rearrangement of the structure led to the hydrolysis of imino and cyano groups probably due to the impossibility of aromatization, as already mentioned.

In conclusion, we synthesized and characterized some pyridazine derivatives (**5,6**) which could represent versatile building blocks for the construction of more complex heterocyclic systems. In particular, the 3-amino-1*H*-pyrazolo[3,4-*c*]pyridazine (**5**), so easily obtained, can be of great importance as analog of purine bases as possible ligands for adenosine receptor subtypes [11], while the simultaneous presence of carbonyl and carboxamido functions on compound **6**, could permit the synthesis of systems of policyclic compounds based on pyridazine nucleus of potential biological interest.[1-4]

Moreover, we isolated in a high yield a really interesting compound, 5-amino-4-cyano-2,3-dihydro-furan-2,3-disulfonic acid disodium salt (**4**), which is worthy of further investigations regarding its reactivity. In fact, it could be a suitable intermediate to obtain other heteroaromatic rings through its reaction with different nucleophiles.



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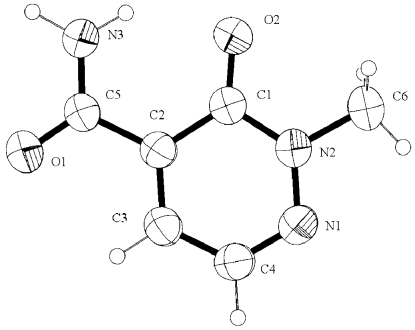
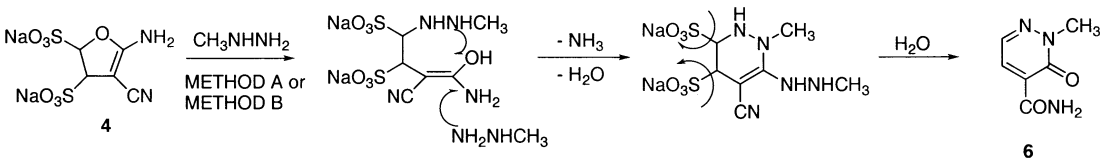


Figure 3. ORTEP [13] view of compound **6** displaying the thermal ellipsoids at 40% probability (for the sake of clarity only one molecule is showed)

Scheme 5



EXPERIMENTAL

Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F_{254} Merck plates) and visualized, when necessary, with aqueous $KMnO_4$. IR spectra were measured on a Perkin-Elmer 500 instrument. ^1H NMR were obtained with a Bruker AC 200 spectrometer, peak positions are given relative to TMS as internal standard, and J values are given in Hz. Melting points were determined on a Buchi-Tottoli instrument and are uncorrected. Chromatography was performed with Merck 40-63 mesh silica gel. All products reported showed IR and ^1H NMR spectra in agreement with the assigned structures.

Crystal Structure Analysis.

X-ray diffraction data were collected on a Nonius Kappa CCD diffractometer at room temperature using graphite-monochromated MoKα radiation (λ = 0.71073 Å) with a ϕ scan followed by ω scan to fill the sphere. Intensities were corrected for Lorentz and polarization. Structures were solved by direct methods with the SIR92 program [12] and refined by full-matrix least squares with anisotropic non-H and isotropic H atoms using the SHELX97 program [13]. ORTEP [14] views of the molecules are showed in Figures 1-3.

5-Amino-4-cyano-2,3-dihydro-furan-2,3-disulfonic Acid Disodium Salt (**4**).

A solution of malononitrile (500 mg, 0.075 mol) in ethanol (10 mL) was added to a suspension of glyoxale bis hydrogen sulfite disodium salt (2.15 g, 0.075 mol) in water (25 mL) and the pH was adjusted around 9 with some drops of aqueous 10% NaOH. The mixture was stirred at room temperature for 4 h; the solvent was removed and the residue was suspended in ethanol (30-40 mL) and the precipitate was collected by filtration to furnish compound **4** (yield 89%); melting point >300 °C; IR (KBr): 3382, 2185, 1681, 1599, 1455, 1215, 1054, 1036, 779, 694. ^1H NMR (D_2O): δ 4.57 (d, 1H, J = 2), 5.53 (d, 1H, J = 2). ^{13}C NMR (D_2O): δ 51.97, 66.84, 93.17, 122.36, 173.11.

Anal. Calcd. for $C_5H_4N_2S_2O_7Na_2 \cdot 3H_2O$: C, 17.39; H, 2.92; N, 8.11. Found: C, 17.37; H, 2.92; N, 8.14.

Crystal Structure Analysis.

4-Cyano-5-amino-2,3-dihydrofuran-2,3-disulfonic acid disodium salt, $[C_5\,H_4\,N_2\,S_2\,O_7]^{2-} \cdot 2Na^+ \cdot 3H_2O$, , *M*r = 368.24, triclinic, space group *P-1*, Z = 2, *a* = 8.1060(2), *b* = 9.3210(3), *c* = 9.8840(3) Å, α = 66.9280(14), β = 89.8960(15), γ = 75.0110(14)°, *V* = 659.56(3) Å^3, ρ_{calc}= 1.854 Mg m^{-3}, *F*(000)= 376, μ = 0.523 mm^{-1}, λ = 0.71069 Å. Total number of reflections measured 8871, unique 3785 (R_{int}= 0.031), 3054 with $I \geq 2\,\sigma\,(I)$ used in the refinement, No parameters = 230, Final R index = 0.0358.

The asymmetric unit consists of a sodium disulfonate salt and three water molecules. Both Na^+ cations are hexa-coordinated, the geometry of the complexes being slightly distorted octahedral, as shown in Figure 1. Na1 binds two water molecules and two sulfonylic oxygens, its coordination being completed by two N1 nitrogens of different asymmetric units, while Na2 is coordinated to six oxygens belonging to three different asymmetric units. Na-O distances are in the range 2.32-2.63 Å and are typical for this type of bond; Na-N distances of 2.344(3) and 2.569(3) Å compare well with those found in hexa-acetonitrile Na complex [15] that are in the range 2.478-2.519 Å. The hydrogens of the amino-group and of the water molecules are implied in a complicated three-dimensional net of hydrogen bonds.

3-Amino-1*H*-pyrazolo[3,4-*c*]pyridazine (**5**).

To a solution of compound **4** (300 mg, 0.81 mmol) in EtOH (20 mL) and water (10 mL) was added hydrazine monohydrate (0.12 mL, 3 eq.) and the mixture was stirred at room temperature for 12 h and then 2 h at 50 °C. The solvent was then removed and the residue was purified by flash chromatography (EtOAc/ Hex 50%) to give compound **5** as a pale yellow solid (yield 57%); melting point 257-259 °C. IR (KBr): 3327, 3049, 1623, 1591, 1169, 1110, 1027, 752. ^1H NMR (DMSO-d_6): δ 5.96 (bs, 2H), 7.99 (d, 1H, J = 6), 8.91 (d, 1H, J = 6), 12.64 (bs, 1H).

Anal. Calcd. for $C_5H_5N_5$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.44; H 3.74; N, 51.87.

Crystal Structure Analysis.

3-Amino-1*H*-pyrazolo[3,4-*c*]pyridazine, $C_5H_5N_5$, *M*r = 135.13, tetragonal, space group *P42/n*, Z = 8, *a* = 17.5850(7), *c* = 3.7465(1) Å, *V* = 1158.54(8) Å^3, ρ_{calc}= 1.549 Mg m^{-3}, *F*(000)= 560, μ = 0.110 mm^{-1}, λ = 0.71069 Å. Total number of reflections measured 8655, unique 1696 (R_{int}= 0.043), 1165 with $I \geq 2\sigma(I)$ used in the refinement. No. Parameters = 111, final R index = 0.0473.

The molecule is almost perfectly planar, with a dihedral angle between the calculated mean-planes of the two fused rings of 1.08(5)°. Molecules related by a centre of symmetry are linked by N3-H…N2 bonds (N…N distance = 2.907(2) Å, N-H…N angle= 169(2)°) and form dimeric units. The N5 aminic nitrogen connects the dimers acting as both a donor and acceptor of hydrogen bonds (N5-H….N4 [y+1/2, -x, z+1/2] = 3.059(2) Å, N5-H….N5[-y, x-1/2, z+1/2] = 3.253(2) Å].

2-Methyl-3-oxo-2,3-dihydro-pyridazine-4-carboxamide (**6**).

Method A.

To a solution of compound **4** (300 mg, 0.81 mmol) in EtOH (20 mL) and water (10 mL) the methyl hydrazine (0.13 mL, 3 eq.) was added and the mixture was stirred at room temperature for 12 h and 2 h at 50 °C. The solvent was then removed and the residue was purified by flash chromatography (EtOAc/ Hex 50%) to give compound **6** as an off-white solid (yield 27%).

Method B.

To a solution of compound **4** (300 mg, 0.81 mmol) in glacial AcOH (20 mL) and water (10 mL), methyl hydrazine (0.086 mL, 3 eq.) was added and the mixture was stirred at reflux for 24 h. The solvent was then removed and the crude was purified by flash chromatography (EtOAc/Hexane 50%) to give compound **6** as an off-white solid (yield 78%); melting point: 156-158 °C. IR (KBr): 3256, 1692, 1621, 1173, 1115. ^1H NMR ($CDCl_3$): δ 3.91 (s, 3H), 7.99 (d, 1H, J = 6), 8.21 (d, 1H, J = 6), 9.42 (bs, 1H).

Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.06; H, 4.61; N, 27.44. Found: C, 47.03; H, 4.62; N, 27.43.

Crystal Structure Analysis.

2-Methyl-3-oxo-2,3-dihydropyridazine-4-carboxamide, $C_6H_7N_3O_2$, *M*r = 153.14, triclinic, space group *P-1*, Z = 2 (two molecules in the asymmetric unit), *a* = 7.500(1), *b* = 8.172(2), *c* = 11.182(3) Å, α = 92.178(8), β = 94.316(7), γ = 96.029(14)°, *V* = 678.9(2) Å^3, ρ_{calc}= 1.508 Mg m^{-3}, *F*(000)= 320, μ = 0.123 mm^{-1},

λ = 0.71069 Å. Total number of reflections measured 3079, unique 2151 (R_{int}= 0.069), 1476 with $I \geq 2\sigma(I)$ used in the refinement. No. parameters= 255, final R index = 0.0661.

In both molecules forming the asymmetric unit the amidic group shows the characteristic delocalization with C-N distances intermediate between double and single bonds (C-N bond lengths = 1.312(4) and 1.318(4) Å). The amidic N forms a short intramolecular hydrogen bond with O2 (N3…O2 = 2.694(4) and 2.696(4) Å, in the two molecules) and an intramolecular N-H…O bonds with O1 (N3….O1a [x, 1-y, -z] = 2.872(4); N3a…O1[-x-1, 1-y, -z] = 2.881(4) Å) linking molecules in infinite antiparallel chains.

Supplementary Material.

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication n. CCDC 203816 (**4**), CCDC 203817 (**5**) and CCDC 203818 (**6**), respectively. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (Fax: Code + (44) 1223 336-033; e-mail: deposit@ccdc.cam.ac.uk)

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