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PYRAN-2-ONES AS SYNTHONS FOR PYRIDAZINE-3-CARBOXYLIC DERIVATIVES. OXIDATION OF NITROGEN-RICH COMPOUNDS[#]

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Abstract – The reaction of 6-(pyridin-2-yl)-2*H*-pyran-2-one (**1**) with hydrazine hydrate toward pyridazine derivatives was investigated. To elucidate the reaction pathway, an intermediary-formed α,δ-dihydrazonohydrazide derivative (**3**) was successfully isolated. Oxidations of the above compounds as well as of other pyridazine derivatives containing a carbohydrazido group, using ammonium cerium(IV) nitrate (CAN), thallium(III) nitrate trihydrate (TTN), or copper(II) acetate hydrate (CuDA), are also presented.

INTRODUCTION

2*H*-Pyran-2-ones and fused pyran-2-ones are useful building blocks in organic synthesis.[1] Several transformations of pyran-2-one derivatives with nucleophiles yielding a variety of heterocyclic systems have been presented. The pyridazines and their fused derivatives are also of considerable interest because of their synthetic potential[2] and diverse pharmacological activities,[3] many of which are related to the cardiovascular system. 1,4-Dihydropyridazines containing 3-carboxylic moieties can be obtained in the cycloaddition reactions of 1,2,4,5-tetrazines with different dienophiles,[4a–d] by the reaction of aminocarbonylazoalkenes with β-tricarbonyl compounds,[4e] *via* the cycloadditions of diazomethane to cyclopropenes,[4f] etc. On the other hand, only a few syntheses of pyridazine derivatives starting from pyran-2-one derivatives have been reported.[5] These syntheses employed diazonium salts as a source of nitrogen fragments.

Since 1,4-dihydropyridazines represent intermediates for aromatic pyridazines, a variety of oxidants[6] have been applied for their dehydrogenation. Among them, CAN,[7] a powerful one-electron oxidant, has already

[#] Dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday.

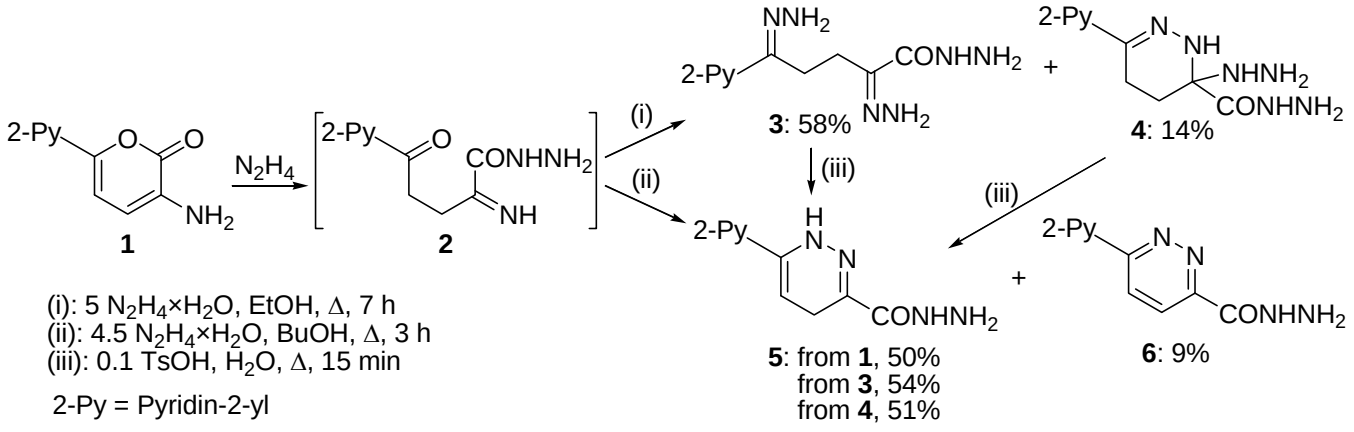
been shown by us to be a very efficient reagent for the cleavage of a hydrazine moiety of carbohydrazides and the aromatization of partially saturated pyridazines.[8]

As part of our ongoing interest in the transformations of 2*H*-pyran-2-ones and fused pyran-2-ones with nucleophilic reagents,[8c,9] we have investigated a new conversion of various 2*H*-pyran-2-ones and fused pyran-2-ones with hydrazine hydrate into the corresponding pyridazine derivatives.[8c,9e] Starting from a pyrano[2,3-*c*]azepine derivative and hydrazine hydrate, we successfully isolated 9a-hydroxy-9-oxo-4,4a,5,6,7,8,9a-octahydro-1*H*-pyridazino[3,4-*c*]azepine-3-carbohydrazide as the key compound for determining the reaction pathway of this conversion.[8c] When non-fused 2*H*-pyran-2-ones were applied in this transformation, different types of products were obtained. We assumed that due to the absence of a fused ring, after the opening of the lactone ring with hydrazine, the formation of a more flexible intermediate could be expected, thus allowing further attacks of additional hydrazine molecules. However, we were not able to detect or isolate any such intermediates.

In this paper we present the reaction of a suitable 2*H*-pyran-2-one derivative with hydrazine hydrate, which afforded the first open-ring intermediate in this transformation. Further reactions of the above products, as well as of other pyridazine derivatives, using different inorganic salts as oxidizing agents, are also reported.

RESULTS AND DISCUSSION

When 6-(pyridin-2-yl)-2*H*-pyran-2-one (**1**) was allowed to react with five equivalents of hydrazine hydrate in boiling ethanol, the α,δ-dihydrazonohydrazide derivative (**3**) was isolated as the main product, accompanied by a small quantity of the 2,3,4,5-tetrahydropyridazine derivative (**4**) (Scheme 1). On the other hand, after refluxing the compound (**1**) in the presence of 4.5 equivalents of hydrazine hydrate in butanol we were able to isolate dihydropyridazine (**5**) in a 1,4-dihydro form (50% yield) and a small amount (9%) of its aromatic analogue (**6**), which is obviously an oxidation product of derivative (**5**) from the oxygen in the air.



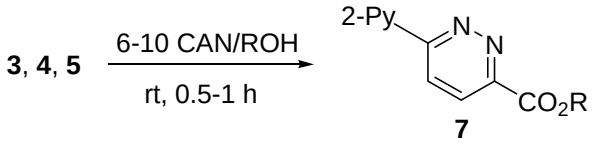
Scheme 1

The structures of the compounds (**3**) and (**4**) were determined on the basis of their NMR data. In the ^{1}H NMR spectrum of **3** two multiplets arising from the coupling of the methylene protons at positions 3 and 4 were found. The singlet signals for the amino groups of the hydrazone moieties were shifted downfield with regard to the amino group of the carbohydrazide (7.05 and 7.37 ppm *vs*. 4.19 ppm), which is also consistent with the literature data.[10] It is important to mention that only three representatives containing a substituted α,δ-dihydrazonohydrazide pattern have been mentioned before,[11] but a re-examination of the structure[12] of two of them has shown that the previously determined structure was not correct. For the third representative two possible structures were offered.[11b] However, our compound (**3**) represents a multifunctional derivative, which is expected to be an interesting synthon for a variety of transformations, because it contains both the unsubstituted hydrazone moieties and the carbohydrazide function.

The mass and elemental analysis of the compound (**4**) revealed the same molecular formula ($C_{10}H_{15}N_7O$) as the compound (**3**), with the only difference being that in the FAB mass spectrum of **4** the [MH^+] peak is relatively weak (21%) and the signal for the [MH^+–N_2H_4] fragment appeared as a basic molecular peak with an intensity of 100%. It seems that this compound contains a labile hydrazine moiety, and as a consequence it is stabilized by the elimination of a hydrazine molecule. Indeed, when the compound (**4**) was treated with 10 mol% of *p*-toluenesulfonic acid in an aqueous solution, the 1,4-dihydropyridazine derivative (**5**) was obtained in a 51% yield (Scheme 1). Furthermore, in the ^{13}C NMR spectrum of the compound (**4**), the signal for 6-C appears at 141.8 ppm and correlates in the ^{1}H–^{13}C HMBC spectrum with the 3'-H of the attached pyridin-2-yl, the 2-H, and the methylene protons (4-CH_2 and 5-CH_2) of the pyridazine moiety.

The formation of the products (**3–5**) from **1** can be explained as follows. We assume that after the opening of the lactone ring of the 2*H*-pyran-2-one (**1**) with hydrazine, yielding the open-ring intermediate (**2**), the attack of two additional hydrazine molecules at the electrophilic carbon atoms of the C=O and C=N groups of **2** takes place, thus leading to the dihydrazonohydrazide derivative (**3**). Furthermore, the compound (**4**) could be formed from **3** by the cyclization of the amino group of the δ-hydrazone moiety with the C=N group of α-hydrazone. Finally, after the elimination of a hydrazine molecule from **4** the dihydropyridazine (**5**) is formed in its 1,4-dihydro form. To support this assumption, the dihydrazone derivative (**3**) was refluxed in butanol for 7 hours; a chromatographic separation of the reaction mixture gave 1,4-dihydropyridazine (**5**) and its aromatic analogue (**6**) in 33% and 19% yields, respectively. On the other hand, the derivative (**5**) was isolated as the sole product in a 54% yield when **3** was heated for a short period of time (15 min) with 10 mol% of *p*-toluenesulfonic acid in an aqueous solution.

To demonstrate the utility of the compound (**3**), it was treated with 6–10 equivalents of CAN in the presence of various alcohols and, after isolation by extraction, pyridazine esters (**7a–c**) were obtained as the sole products (Scheme 2, Runs 1, 2, and 3, Table 1) in 51–71% yields.



Scheme 2

Table 1. Oxidations of compounds (**3**–**5**) with CAN in the presence of various alcohols.

Run	Compound	R	React. time[a] (h)	Product (yield; %)[b]
1	**3**	Me	1	**7a** (59)[c], (71)[d]
2	**3**	Et	1	**7b** (51)[c]
3	**3**	*i*-Pr	1	**7c** (58)[c]
4	**4**	Me	0.5	**7a** (70)[c]
5	**5**	Me	0.5	**7a** (98)[c]

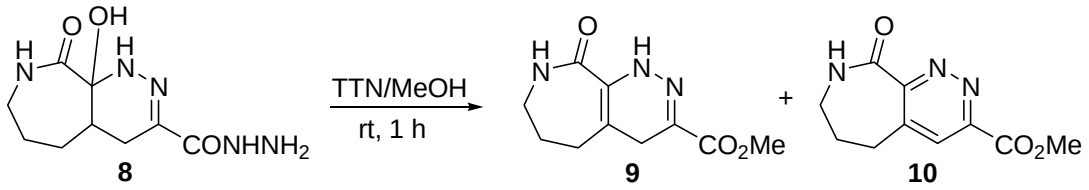
[a]Reaction time after the addition of the entire amount of the compound (**3**), (**4**) or (**5**) to the mixture of CAN in alcohol. [b]Yields of isolated products are given. [c]6 Equiv. of CAN was used. [d]10 Equiv. of CAN was used.

It is obvious that the oxidation of the hydrazide function of **3** was accompanied by cyclization, the elimination of a hydrazine molecule, and the dehydrogenation of a 1,4-dihydropyridazine ring.

One might assume that due to the acidic medium of the reaction mixture, the dihydrazone derivative (**3**) in the first step undergoes an acid-catalyzed cyclocondensation into a 1,4-dihydropyridazine intermediate, which is further oxidized to the pyridazine esters (**7a**–**c**). This assumption was unambiguously confirmed by a treatment of the compound (**3**) with a catalytic amount of *p*-toluenesulfonic acid, resulting in its conversion to the corresponding 1,4-dihydropyridazine derivative (**5**), as described above (Scheme 1). Oxidation of 2,3,4,5-tetrahydropyridazine (**4**) with CAN in a methanolic solution gave methyl pyridazine-3-carboxylate (**7a**) in 70% yield (Run 4, Table 1). Here again, an initially acid-catalyzed elimination of hydrazine from the compounds (**4**) could be proposed (as mentioned above), followed by a further oxidation leading to **7a**. Additionally, the compound (**5**) was also smoothly converted to the methyl pyridazine-3-carboxylate in 98% yield by the oxidation with CAN in a methanolic solution (Run 5, Table 1).

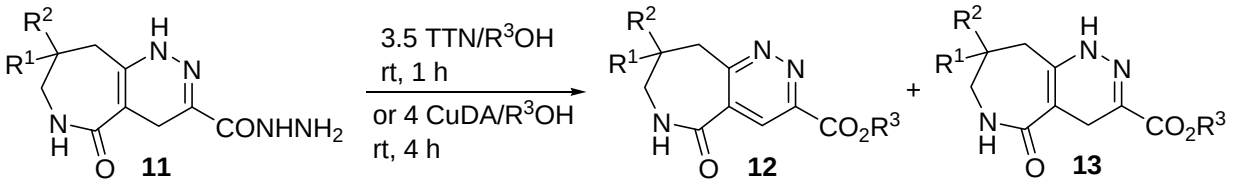
Since CAN successfully oxidized both a 1,4-dihydropyridazine ring and a carbohydrazido group and did not show any selectivity,[8b,c] we wanted to check the oxidation ability of other oxidants in order to achieve the selective oxidation of just the carbohydrazido moiety. For this purpose we performed oxidation in the pyridazino[3,4-*c*]azepine series with TTN. When applying 1.5 equivalents of TTN in a methanolic solution of **8**,[8c] a mixture of methyl esters (**9**) and (**10**) was isolated and separated by column chromatography to give the compound (**9**) as the major product (Scheme 3). With a larger amount of TTN

(3.5 equivalents), an aromatic pyridazine ester (**10**) was isolated as the sole product. We can assume that an acidic medium catalyses the elimination of a water molecule from the compound (**8**) during the oxidation with TTN, thus initially giving the 1,4-dihydropyridazine ester (**9**), which is further dehydrogenated and transformed to the aromatic pyridazine ester (**10**). Using CAN, however, we did not isolate a partially oxidized product (**9**).[8c]



Scheme 3

We have preliminarily reported that the oxidation of the 1,4-dihydropyridazino[4,3-*c*]azepines (**11**) with CuDA in methanol gave the mixture of esters (**12**) and (**13**),[9e] despite of an excess of the oxidant (7 equiv.) and long reaction times (up to 17 h). It is reasonable to assume that the reaction with a smaller amount of CuDA in a shorter time might result in the selective oxidation of just the hydrazide moiety.



Scheme 4

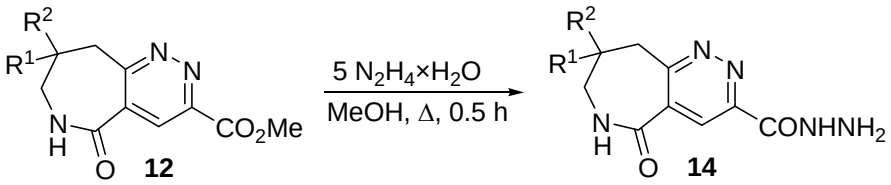
Table 2. Oxidation of 1,4-dihydropyridazino[4,3-*c*]azepines (**11**) with TTN or CuDA.

Run	R^1	R^2	R^3	Product (yield; %) with TTN[a]	Products (yield; %)[b] with CuDA
1	H	H	Me	**12a** (72%)	**12a** (12), **13a** (36)
2	H	Me	Me	**12b** (60%)	**12b** (17), **13b** (37)
3	Me	Me	Me	**12c** (62%)	-
4	H	H	Et	-	**12d** (8), **13d** (26)
5	H	Me	Et	-	**12e** (15), **13e** (50)
6	Me	Me	Et	-	**12f** (19), **13f** (46)

[a]For comparison, previously reported results[9e] are given. [b]Yields of products, isolated by column chromatography, are given.

After treating the compounds (**11**) with four equivalents of CuDA in the presence of methanol or ethanol for 4 h, the separation of the reaction mixture by column chromatography afforded, in all cases, mixtures of the esters (**12**) and (**13**), the latter being predominant (Scheme 4, Table 2).

We reported previously that in the reaction of pyrano[3,2-*c*]azepines with hydrazine hydrate toward the 1,4-dihydropyridazino[4,3-*c*]azepines (**11**) a small quantity of by-products (**14**) was also formed, presumably as oxidation products of **11** by the air.[9e] Their structure was proposed only on the basis of the ^{1}H NMR spectra of the crude reaction mixtures. Now we report on an independent synthesis of these products. Namely, the methoxy group in the methyl esters (**12**) was replaced with the hydrazine moiety during brief heating with an excess of hydrazine hydrate in a methanolic solution yielding the pyridazino[4,3-*c*]azepine-3-carbohydrazides (**14**) in 51–80% yields (Scheme 5, Table 3).



Scheme 5

Table 3. Reaction of methyl esters (**13**) with hydrazine hydrate.

Run	R^1	R^2	Product (yield; %)[a]
1	H	H	**14a** (80)
2	H	Me	**14b** (51)
3	Me	Me	**14c** (57)

[a]Yields of isolated products are given.

In conclusion, we have presented a detailed investigation of the transformation of the 2*H*-pyran-2-one derivative (**1**) with hydrazine hydrate and have unequivocally shown that the α,δ-dihydrazonohydrazide derivative (**3**) can appear as an intermediate in this reaction, leading to 1,4-dihydropyridazine derivatives as final products. We checked the oxidation ability of different oxidants in the transformations of different pyridazine derivatives and found that TTN and CuDA exhibited a certain degree of selectivity in the oxidation of a partially saturated pyridazine ring containing a carbohydrazide moiety, whereas CAN gave the aromatic pyridazine esters as the sole products without exhibiting any selectivity. The reported transformations may be important from the point of view of the growing interest in various biologically active pyridazine derivatives.[3] We have also verified that the investigated method could be successfully applied for the preparation of differently substituted pyridazines. Though the synthesis of some of the starting compounds used in our investigation has not yet been completely described, they can be easily available by known methods.[14]

EXPERIMENTAL

Starting **1** was prepared from previously known 3-benzoylamino-2*H*-pyran-2-one[13a] using a known method.[13b,c] The compounds (**8**)[8c] and (**11**)[9e] were prepared as described earlier. All the other reagents and solvents were used as obtained from commercial suppliers. Melting points were determined on a Kofler micro hot stage, and are uncorrected. ^{1}H and ^{13}C spectra were recorded at 29 ºC in DMSO-d_6 with a Bruker Avance DPX 300 spectrometer, using TMS as an internal standard. ^{13}C NMR spectra are referenced against the central line of DMSO-d_6 at δ = 39.5 ppm. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Bio-Rad FTS 3000 MX spectrophotometer. MS spectra were recorded with a VG-Analytical AutoSpec Q instrument. Elemental analyses (C, H, N) were performed with a Perkin-Elmer 2400 CHNS/O analyzer. TLC was carried out on Fluka silica-gel TLC-cards. Column chromatography was carried out with Fluka silica-gel 60 (220-440 mesh).

Synthesis of 3 and 4. A mixture of **1** (940 mg, 5 mmol), hydrazine hydrate (1.277 g, 98%, 25 mmol) and absolute EtOH (20 mL) was refluxed for 7 h, after which it was left at rt for 1 day. The crystals were collected by filtration and washed with EtOH to give **3** (721 mg, 58%). The filtrate was evaporated under reduced pressure to dryness and MeOH (5 mL) was added. Upon cooling, the precipitate was filtered off and washed with MeOH to provide **4** (176 mg, 14%).

Synthesis of 5 and 6. A mixture of **1** (376 mg, 2 mmol), hydrazine hydrate (460 mg, 98%, 9 mmol) and BuOH (8 mL) was refluxed for 3 h. The solvent was evaporated *in vacuo* and subsequent column chromatography ($CHCl_3$/MeOH 25:1) of the solid residue resulted in **5** (218 mg, 50%) and **6** (39 mg, 9%).

Transformation of 3 and 4 to 5. A mixture of **3** or **4** (1 mmol), *p*-toluenesulfonic acid hydrate (19 mg, 0.1 mmol) and water (3 mL) was refluxed for 15 min. Upon cooling, the precipitate was collected by filtration and washed with a small amount of water affording **5**. Yields: from **3** (117 mg, 54%), from **4** (111 mg, 51%).

Transformation of 3 to 5 and 6. A mixture of **3** (249 mg, 1 mmol) and BuOH (5 mL) was refluxed for 7 h. The solvent was evaporated *in vacuo* and subsequent column chromatography ($CHCl_3$/MeOH 25:1) of the solid residue resulted in **5** (71 mg, 33%) and **6** (41 mg, 19%).

General procedure for the oxidation of 3, 4, and 5 with CAN. To a stirred mixture of CAN (for quantities, see Table 1) in an alcohol (10–15 mL) at rt **3, 4**, or **5** (1 mmol) was added over a period of 10–20 min and stirring was continued for 0.5–1 h. Then the solvent was removed under reduced pressure, the solid residue was treated with water (10 mL) and the aqueous mixture was extracted with CH_2Cl_2 (6×10 mL). The collected organic layers were dried over anhydrous Na_2SO_4 and evaporated *in vacuo*, affording **7**. Yields are given in Table 1.

Oxidation of 8 with TTN. To a stirred mixture of **8** (482 mg, 2 mmol) in MeOH (30 mL) at rt, a solution of TTN (3 mmol or 7 mmol) in MeOH (14 mL) was added and stirred for 1 h. The solid was filtered off, the filtrate was evaporated in *vacuo*, and the residue was diluted with water (40 mL) and extracted with $CHCl_3$ (6×30 mL). Collected organic layers were dried over anhydrous Na_2SO_4. After evaporation **10** was obtained as the white product or the crude mixture of products was separated by column chromatography ($CHCl_3$/MeOH 25:1) to afford **9** and **10**. Yields are given in Scheme 3.

General procedure for the oxidation of 11 with CuDA. A mixture of **11** (1 mmol), copper(II) acetate monohydrate (799 mg, 4 mmol) and alcohol (20 mL) was stirred at rt for 4 h. Then the reaction mixture was evaporated and the solid residue was extracted with hot $CHCl_3$ (3×30 mL). The exctract was subjected to purification by column chromatography ($CHCl_3$/MeOH = 19/1) to afford **12** and **13**. Yields are given in Table 2.

General procedure for the preparation of 14. A mixture of **12** (1 mmol), hydrazine hydrate (255 mg, 5 mmol, 98%) and MeOH (5 mL) was refluxed for 0.5 h. Upon cooling the precipitate was filtered off and washed with a small amount of MeOH to give **14**. Yields are given in Table 3.

Analytical and spectroscopic data of products:

2,5-Dihydrazono-5-(pyridin-2-yl)pentanohydrazide (3): mp 141–144 °C (EtOH); IR (KBr) ν_{max}/cm^{-1}: 3406, 3382, 3309, 3226, 3154, 1651, 1642, 1614, 1580, 1493; ^{1}H NMR (300 MHz): δ2.50 (m, 2H, 3-CH_2), 2.75 (m, 2H, 4-CH_2), 4.19 (s, 2H, NH_2), 7.05 (s, 2H, NNH_2), 7.23 (ddd, J_1=1.1, J_2=4.9, J_3=7.4 Hz, 1H, 5'-H), 7.37 (s, 2H, NNH_2), 7.71 (ddd, J_1=1.8, J_2=7.4, J_3=8.2 Hz, 1H, 4'-H), 7.86 (ddd, J_1=1.1, J_2=1.1, J_3=8.2 Hz, 1H, 3'-H), 8.46 (ddd, J_1=1.1, J_2=1.8, J_3=4.9 Hz, 1H, 6'-H), 8.67 (br s, 1H, NH); ^{13}C NMR (75.5 MHz): δ18.3, 18.6, 118.7, 121.8, 136.2, 137.8, 143.7, 147.9, 156.1, 164.9; MS (*m/z*, %) 250 (MH^+, 32), 79 (100). *Anal*. Calcd for $C_{10}H_{15}N_7O$: C, 48.18; H, 6.07; N, 39.33. Found: C, 48.43; H, 6.22; N, 39.57.

3-Hydrazino-6-(pyridin-2-yl)-2,3,4,5-tetrahydropyridazine-3-carbohydrazide (4): mp 117–121 °C (MeOH); IR (KBr) ν_{max}/cm^{-1}: 3308, 3266, 3160, 1667, 1601, 1581; ^{1}H NMR (300 MHz): δ1.80 (m, 1H, 4-H_a), 1.94 (m, 1H, 4-H_b), 2.62 (m, 2H, 5-CH_2), 3.31 (br s, 2H, NH_2), 4.12 (br s, 1H, NH), 4.25 (br s, 2H, NH_2), 7.22 (ddd, J_1=1.1, J_2=4.9, J_3=7.4 Hz, 1H, 5'-H), 7.53 (s, 1H, 2-H), 7.70 (ddd, J_1=1.8, J_2=7.4, J_3=8.1 Hz, 1H, 4'-H), 7.84 (ddd, J_1=1.1, J_2=1.1, J_3=8.1 Hz, 1H, 3'-H), 8.47 (ddd, J_1=1.1, J_2=1.8, J_3=4.9 Hz, 1H, 6'-H), 9.02 (br s, 1H, NH); ^{13}C NMR (75.5 MHz): δ18.5, 24.6, 72.4, 118.0, 122.0, 135.8, 141.8, 148.2, 155.8, 171.2; MS (*m/z*, %) 250 (MH^+, 21), 218 (100). *Anal*. Calcd for $C_{10}H_{15}N_7O$: C, 48.18; H, 6.07; N, 39.33. Found: C, 48.37; H, 6.29; N, 39.47.

6-(Pyridin-2-yl)-1,4-dihydropyridazine-3-carbohydrazide (5): mp 150–153 °C (EtOAc/hexane); IR (KBr) ν_{max}/cm^{-1}: 3422, 3310, 3222, 1682, 1647, 1605, 1592, 1566; ^{1}H NMR (300 MHz): δ3.08 (d, *J*=4.2

Hz, 2H, 4-CH_2), 4.31 (s, 2H, NH_2), 5.58 (dt, J_1=1.9, J_2=4.2 Hz, 1H, 5-H), 7.37 (ddd, J_1=1.2, J_2=4.8, J_3=7.2 Hz, 1H, 5'-H), 7.78 (ddd, J_1=1.2, J_2=1.2, J_3=8.1 Hz, 1H, 3'-H), 7.85 (ddd, J_1=1.7, J_2=7.2, J_3=8.1 Hz, 1H, 4'-H), 8.57 (ddd, J_1=1.2, J_2=1.7, J_3=4.8 Hz, 1H, 6'-H), 9.04 (s, 1H, NH), 9.51 (d, J=1.9 Hz, 1H, 1-H); ^{13}C NMR (75.5 MHz): δ21.0, 94.6, 119.1, 123.3, 133.7, 136.9, 137.1, 148.4, 149.7, 163.6; MS (*m/z*, %) 217 (M^+, 24), 201 (100). *Anal*. Calcd for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.10; N, 32.24. Found: C, 55.39; H, 5.29; N, 32.34.

6-(Pyridin-2-yl)pyridazine-3-carbohydrazide (6): mp 198–199 °C (MeOH); IR (KBr) ν_{max}/cm^{-1}: 3386, 3316, 3210, 3091, 1668, 1611, 1589, 1500; ^{1}H NMR (300 MHz): δ4.79 (br s, 2H, NH_2), 7.61 (ddd, J_1=1.0, J_2=4.8, J_3=7.7 Hz, 1H, 5'-H), 8.07 (ddd, J_1=1.8, J_2=7.7, J_3=7.9 Hz, 1H, 4'-H), 8.29 (d, J=8.8 Hz, 1H, 4-H), 8.62 (ddd, J_1=1.0, J_2=1.0, J_3=7.9 Hz, 1H, 3'-H), 8.69 (d, J=8.8 Hz, 1H, 5-H), 8.80 (ddd, J_1=1.0, J_2=1.8, J_3=4.8 Hz, 1H, 6'-H), 10.47 (s, 1H, NH); ^{13}C NMR (75.5 MHz): δ121.4, 125.3, 125.5, 126.3, 137.8, 149.9, 152.3, 152.8, 158.9, 161.1; MS (*m/z*, %) 215 (M^+, 100). *Anal*. Calcd for $C_{10}H_9N_5O$: C, 55.81; H, 4.22; N, 32.54. Found: C, 56.00; H, 4.50; N, 32.48.

Methyl 6-(Pyridin-2-yl)pyridazine-3-carboxylate (7a): mp 162.5–164 °C (MeOH/H_2O); IR (KBr) ν_{max}/cm^{-1}: 3073, 2951, 1713, 1589, 1575; ^{1}H NMR (300 MHz): δ4.01 (s, 3H, Me), 7.62 (ddd, J_1=1.0, J_2=4.9, J_3=7.8 Hz, 1H, 5'-H), 8.09 (ddd, J_1=1.8, J_2=7.8, J_3=7.8 Hz, 1H, 4'-H), 8.36 (d, J=8.9 Hz, 1H, 4-H), 8.65 (ddd, J_1=1.0, J_2=1.0, J_3=7.8 Hz, 1H, 3'-H), 8.70 (d, J=8.9 Hz, 1H, 5-H), 8.81 (ddd, J_1=1.0, J_2=1.8, J_3=4.9 Hz, 1H, 6'-H); ^{13}C NMR (75.5 MHz): δ52.9, 121.7, 125.0, 125.8, 128.8, 137.8, 150.0, 151.0, 152.0, 159.3, 164.1; MS (*m/z*, %) 215 (M^+, 27), 157 (100). *Anal*. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.67; H, 4.30; N, 19.77.

Ethyl 6-(Pyridin-2-yl)pyridazine-3-carboxylate (7b): mp 116–118 °C (MeOH/H_2O); IR (KBr) ν_{max}/cm^{-1}: 1720, 1708, 1590, 1572, 1370, 1302; ^{1}H NMR (300 MHz): δ1.40 (t, J=7.2 Hz, 3H, CH_2CH_3), 4.47 (q, J=7.2 Hz, 2H, CH_2CH_3), 7.63 (ddd, J_1=1.0, J_2=4.8, J_3=7.7 Hz, 1H, 5'-H), 8.09 (ddd, J_1=1.8, J_2=7.7, J_3=7.9 Hz, 1H, 4'-H), 8.36 (d, J=8.9 Hz, 1H, 4-H), 8.65 (ddd, J_1=1.0, J_2=1.0, J_3=7.9 Hz, 1H, 3'-H), 8.70 (d, J=8.9 Hz, 1H, 5-H), 8.81 (ddd, J_1=1.0, J_2=1.8, J_3=4.8 Hz, 1H, 6'-H); ^{13}C NMR (75.5 MHz): δ14.0, 61.9 121.7, 124.9, 125.7, 128.7, 137.8, 149.9, 151.2, 152.0, 159.2, 163.5; MS (*m/z*, %) 229 (M^+, 6), 79 (100). *Anal*. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.60; H, 5.11; N, 18.52.

Isopropyl 6-(Pyridin-2-yl)pyridazine-3-carboxylate (7c): mp 132–135 °C (MeOH/H_2O); IR (KBr) ν_{max}/cm^{-1}: 3059, 2978, 1717, 1590, 1574; ^{1}H NMR (300 MHz): δ1.41 (d, J=6.2 Hz, 6H, $CHMe_2$), 5.29 (septet, J=6.2 Hz, 1H, $CHMe_2$), 7.62 (ddd, J_1=1.1, J_2=4.8, J_3=7.6 Hz, 1H, 5'-H), 8.09 (ddd, J_1=1.8, J_2=7.6, J_3=7.8 Hz, 1H, 4'-H), 8.34 (d, J=9.0 Hz, 1H, 4-H), 8.65 (ddd, J_1=1.1, J_2=1.1, J_3=7.8 Hz, 1H, 3'-H), 8.69 (d, J=9.0 Hz, 1H, 5-H), 8.81 (ddd, J_1=1.1, J_2=1.8, J_3=4.8 Hz, 1H, 6'-H); ^{13}C NMR (75.5 MHz): δ21.5,

69.7, 121.7, 124.9, 125.7, 128.6, 137.8, 149.9, 151.4, 152.0, 159.2, 163.0; MS (*m/z*, %) 244 (MH^+). *Anal*. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 63.91; H, 5.53; N 17.18.

Methyl 9-Oxo-4,5,6,7,8,9-hexahydro-1*H*-pyridazino[3,4-*c*]azepine-3-carboxylate (9): mp 150–154 °C (EtOAc); IR (KBr) ν_{max}/cm^{-1}: 3369, 3328, 1722, 1696, 1626; ^1H NMR (300 MHz): δ1.82 (m, 2H, 6-CH_2), 2.30 (m, 2H, 5-CH_2), 2.96 (s, 2H, 4-CH_2), 3.08 (m, 2H, 7-CH_2), 3.70 (s, 3H, Me), 8.16 (t, *J*=4.8 Hz, 1H, 8-H), 9.55 (s, 1H, 1-H); ^{13}C NMR (75.5 MHz): δ27.4, 27.6, 32.9, 40.1, 51.6, 114.7, 126.6, 127.6, 164.1, 164.7; MS (*m/z*, %) 223 (M^+, 66), 163 (100). *Anal.* Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 54.06; H, 5.84; N, 18.87.

Methyl 9-Oxo-6,7,8,9-tetrahydro-5*H*-pyridazino[3,4-*c*]azepine-3-carboxylate (10): mp 206–208 °C (EtOH) (lit.,[8c] mp 206–208 °C).

Methyl 5-Oxo-6,7,8,9-tetrahydro-5*H*-pyridazino[4,3-*c*]azepine-3-carboxylate (12a): mp 221–224 °C (MeOH) (lit.,[8b,9e] mp 221–224 °C).

Methyl 8-Methyl-5-oxo-6,7,8,9-tetrahydro-5*H*-pyridazino[4,3-*c*]azepine-3-carboxylate (12b): mp 143–145 °C (Et_2O) (lit.,[8b,9e] mp 143–145 °C).

Ethyl 5-Oxo-6,7,8,9-tetrahydro-5*H*-pyridazino[4,3-*c*]azepine-3-carboxylate (12d): mp 146–150 °C (EtOAc/Et_2O) (lit.,[8b] mp 146–150 °C).

Ethyl 8-Methyl-5-oxo-6,7,8,9-tetrahydro-5*H*-pyridazino[4,3-*c*]azepine-3-carboxylate (12e): mp 129–133 °C (EtOAc/Et_2O) (lit.,[8b] mp 129–133 °C).

Ethyl 8,8-Dimethyl-5-oxo-6,7,8,9-tetrahydro-5*H*-pyridazino[4,3-*c*]azepine-3-carboxylate 12f: mp 122–125 °C (EtOAc/Et_2O) (lit.,[8b] mp 122–125 °C).

Methyl 5-Oxo-4,5,6,7,8,9-hexahydro-1*H*-pyridazino[4,3-*c*]azepine-3-carboxylate (13a): mp 195–199 °C (EtOAc/MeOH); IR (KBr) ν_{max}/cm^{-1}: 3272, 3192, 3076, 3028, 2957, 1727, 1654, 1607, 1513; ^1H NMR (300 MHz): δ1.81 (m, 2H, 8-CH_2), 2.36 (m, 2H, 9-CH_2), 3.02 (s, 2H, 4-CH_2), 3.03 (m, 2H, 7-CH_2), 3.72 (s, 3H, Me), 7.49 (deg t, 1H, 6-H), 10.16 (s, 1H, 1-H); ^{13}C NMR (75.5 MHz): δ21.6, 27.1, 27.8, 39.5, 51.8, 96.5, 133.5, 142.2, 164.5, 171.0; MS (*m/z*, %) 223 (M^+, 100). *Anal.* Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.58; H, 5.70; N, 18.69.

Methyl 8-Methyl-5-oxo-4,5,6,7,8,9-hexahydro-1*H*-pyridazino[4,3-*c*]azepine-3-carboxylate (13b): mp 172–175 °C (EtOAc/MeOH); IR (KBr) ν_{max}/cm^{-1}: 3305, 3187, 1720, 1657, 1639, 1610; ^1H NMR (300 MHz): δ0.86 (d, *J*=6.8 Hz, 3H, Me), 1.99 (m, 1H, 9-H_a), 2.16 (m, 1H, 8-H), 2.42 (m, 1H, 9-H_b), 2.65 (m, 1H, 7-H_a), 3.00 (s, 2H, 4-CH_2), 3.07 (m, 1H, 7-H_b), 3.71 (s, 3H, OMe), 7.49 (t, *J*=5.3 Hz, 1H, 6-H), 10.20(s, 1H, 1-H); MS (*m/z*, %) 237 (M^+, 100). *Anal.* Calcd for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.56; H, 6.39; N, 17.46.

Ethyl 5-Oxo-4,5,6,7,8,9-hexahydro-1*H*-pyridazino[4,3-*c*]azepine-3-carboxylate (13d): mp 199–200°C

(EtOAc/MeOH); IR (KBr) ν_{max}/cm^{-1}: 3274, 3243, 3200, 2976, 1704, 1656, 1612; ^1H NMR (300 MHz): δ1.24 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.81 (m, 2H, 8-CH_2), 2.36 (m, 2H, 9-CH_2), 3.01 (s, 2H, 4-CH_2), 3.02 (m, 2H, 7-CH_2), 4.18 (q, *J*=7.2 Hz, 2H, CH_2CH_3), 7.49 (t, *J*=5.0 Hz, 1H, 6-H), 10.14 (s, 1H, 1-H); ^{13}C NMR (75.5 MHz): δ14.1, 21.5, 27.1, 27.8, 60.5, 96.5, 133.7, 142.3, 164.0, 171.0 (one carbon signal is missing); MS (*m/z*, %) 237 (M^+, 100). *Anal.* Calcd for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.93; H, 6.31; N, 17.60.

Ethyl 8-Methyl-5-oxo-4,5,6,7,8,9-hexahydro-1*H*-pyridazino[4,3-*c*]azepine-3-carboxylate (13e): mp 185–187 °C (EtOAc/MeOH); IR (KBr) ν_{max}/cm^{-1}: 3293, 3198, 2961, 1715, 1657, 1632, 1615; ^1H NMR (300 MHz): δ0.86 (d, *J*=6.8 Hz, 3H, Me), 1.24 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.99 (m, 1H, 9-H_a), 2.16 (m, 1H, 8-H), 2.42 (m, 1H, 9-H_b), 2.65 (m, 1H, 7-H_a), 3.00 (s, 2H, 4-CH_2), 3.07 (m, 1H, 7-H_b), 4.18 (q, *J*=7.1 Hz, 2H, CH_2CH_3), 7.49 (t, *J*=5.3 Hz, 1H, 6-H), 10.18 (s, 1H, 1-H); ^{13}C NMR (75.5 MHz): δ14.1, 18.8, 21.2, 34.0, 34.6, 46.3, 60.5, 96.5, 133.5, 141.3, 164.1, 171.8; MS (*m/z*, %) 251 (M^+, 100). *Anal.* Calcd for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.23; H, 6.49; N, 16.82.

Ethyl 8,8-Dimethyl-5-oxo-4,5,6,7,8,9-hexahydro-1*H*-pyridazino[4,3-*c*]azepine-3-carboxylate (13f): mp 183.5–186.5 °C (EtOAc/MeOH); IR (KBr) ν_{max}/cm^{-1}: 3289, 3183, 2963, 1720, 1651, 1633, 1611; ^1H NMR (300 MHz): δ0.90 (s, 6H, two Me), 1.24 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 2.03 (s, 2H, 9-CH_2), 2.70 (d, *J*=5.4 Hz, 2H, 7-CH_2), 3.01 (s, 2H, 4-CH_2), 4.18 (q, *J*=7.1 Hz, 2H, CH_2CH_3), 7.58 (t, *J*=5.4 Hz, 1H, 6-H), 10.22 (s, 1H, 1-H); ^{13}C NMR (75.5 MHz): δ14.1, 21.0, 26.4, 39.6, 39.8, 52.1, 60.5, 96.6, 133.5, 141.3, 164.1, 172.4; MS (*m/z*, %) 265 (M^+, 100). *Anal.* Calcd for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 59.06; H, 7.47; N, 15.59.

5-Oxo-6,7,8,9-tetrahydro-5*H*-pyridazino[4,3-*c*]azepine-3-carbohydrazide (14a): mp 225–227°C (MeOH); IR (KBr) ν_{max}/cm^{-1}: 3292br, 3192, 3053, 1676, 1616, 1468, 1418; ^1H NMR (300 MHz): δ2.08 (m, 2H, 8-CH_2), 3.01 (m, 2H, 7-CH_2), 3.21 (m, 2H, 9-CH_2), 4.70 (br s, 2H, NH_2), 8.07 (s, 1H, 4-H), 8.60 (t, *J*=5.5 Hz, 1H, 6-H), 10.41 (s, 1H, NH); ^{13}C NMR (75.5 MHz): δ28.6, 30.2, 38.0, 123.8, 134.8, 153.0, 159.3, 160.9, 167.8; MS (*m/z*, %) 221 (M^+, 100). *Anal*. Calcd for $C_9H_{11}N_5O_2$: C, 48.87; H, 5.01; N, 31.66. Found: C, 48.96; H, 4.84; N, 31.62.

8-Methyl-5-oxo-6,7,8,9-tetrahydro-5*H*-pyridazino[4,3-*c*]azepine-3-carbohydrazide (14b): mp 226–228 °C (MeOH); IR (KBr) ν_{max}/cm^{-1}: 3325, 3210br, 3081, 1682, 1640, 1516, 1463, 1420; ^1H NMR (300 MHz): δ0.98 (d, *J*=6.8 Hz, 3H, Me), 2.44 (m, 1H, 8-H), 2.61 (m, 1H, 7-H_a), 2.83 (m, 1H, 9-H_a), 3.06 (m, 1H, 7-H_b), 3.31 (m, 1H, 9-H_b), 4.69 (s , 2H, NH_2), 8.07 (s, 1H, 4-H), 8.67 (t, *J*=5.6 Hz, 1H, 6-H), 10.40 (br s, 1H, NH); ^{13}C NMR (75.5 MHz): δ18.2, 35.0, 37.9, 44.7, 123.7, 134.7, 153.0, 158.7, 160.9, 167.7; MS (*m/z*, %) 235 (M^+, 100). *Anal*. Calcd for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57; N, 29.77. Found: C, 51.01; H, 5.45; N, 29.67.

8,8-Dimethyl-5-oxo-6,7,8,9-tetrahydro-5*H*-pyridazino[4,3-*c*]azepine-3-carbohydrazide (14c): mp 246–250 °C (MeOH); IR (KBr) ν_{max}/cm^{-1}: 3322, 3261, 3183, 3058, 2962, 2927, 1686br, 1634, 1513, 1467; ^{1}H NMR (300 MHz): δ1.00 (s, 6H, two Me), 2.64 (d, *J*=6 Hz, 2H, 7-CH_2), 2.92 (s, 2H, 9-CH_2), 4.70 (br s, 2H, NH_2), 8.07 (s, 1H, 4-H), 8.78 (t, *J*=6 Hz, 1H, 6-H), 10.40 (br s, 1H, NH); ^{13}C NMR (75.5 MHz): δ25.7, 39.6, 44.2, 50.2, 123.7, 134.5, 152.9, 158.7, 161.0, 167.7; MS (*m/z*, %) 249 (M^+, 100). *Anal*. Calcd for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.10. Found: C, 52.96; H, 5.94; N, 28.05.

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14. In the near future we plan to publish in all the details the synthesis and characterization of the starting compounds applied in this and previous study.[8c]