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ScienceDirect
Tetrahedron
Tetrahedron 62 (2006) 9718–9725

The synthesis of heterocyclic derivatives from pyran-2-ones and hydrazine hydrate. Ammonium cerium(IV) nitrate as an efficient oxidant in pyridazine chemistry

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Received 24 April 2006; revised 4 July 2006; accepted 20 July 2006
Available online 10 August 2006

Dedicated to Professor Miha Tišler on the occasion of his 80th birthday

Abstract—A novel reaction of 3-amino-2*H*-pyran-2-ones and their fused derivatives with hydrazine hydrate leading to the corresponding pyridazine derivatives is reported. Further oxidation with ammonium cerium(IV) nitrate (CAN, from Cerium(IV) Ammonium Nitrate) yields a collection of pyridazine-3-carboxylates.

1. Introduction

Pyridazines and fused pyridazines are of considerable interest because of their synthetic utility[1] and important pharmacological activities,[2] many of them related to the cardiovascular system. 1,4-Dihydropyridazine derivatives including their carboxylic esters can be obtained in the cycloaddition reactions of 1,2,4,5-tetrazines with different dienophiles,[3] by the reaction of aminocarbonylazoalkenes with β-tricarbonyl compounds,[4] via the cycloaddition of diazomethane to cyclopropenes,[5] etc. Since the 1,4-dihydropyridazine system represents an intermediate for aromatized pyridazines, a plethora of inorganic and organic oxidants have been found to readily dehydrogenate dihydropyridazines.[3c,d,4,5,6] Among them, CAN,[7] a powerful one-electron oxidant, which has already shown great utility in carbon–carbon[7a] or carbon–heteroatom[7b] bond-forming reactions, was previously used as a reagent for the cleavage of the hydrazine moiety of carbohydrazides.[8] Recently, we have also reported on its applicability as an oxidant for 1,4,6,7,8,9-hexahydro-5*H*-pyridazino[4,3-*c*]azepine-3-carboxylic acid hydrazides in the presence of an alcohol, where both the pyridazine moiety and the carbohydrazido group were successfully oxidized, resulting in the corresponding aromatic pyridazine esters.[9] The main advantages of CAN are its experimental simplicity, easy handling, non-toxicity, and solubility in many common organic solvents.

Many transformations of pyran-2-ones with nucleophilic reagents yielding different types of products have been investigated.[10] As part of our continuing interest in the transformations of pyran-2-one derivatives with hydrazine and its derivatives[11] we preliminarily reported on a new conversion of pyrano[3,2-*c*]azepines with hydrazine hydrate into representatives of pyridazino[4,3-*c*]azepines.[11e] The presence of a free amino group at position 3 in the starting pyran-2-ones was found to be crucial for the synthesis of pyridazine derivatives, because all other fused pyran-2-ones, possessing a benzoyl-protected amino group, led in the reaction with hydrazine hydrate (or its derivatives) to different products: to fused pyridine derivatives,[11a,b] in some cases the reaction took place at the side group,[11b,d,g,h] in other cases β-heteroaryl-α,β-didehydro-α-amino acid derivatives were obtained.[11c,h,i] In this paper we report on the exploration of the scope and limitations of the reaction starting from a variety of 2*H*-pyran-2-ones and fused pyran-2-ones, bearing a free amino group at position 3, with hydrazine hydrate into representatives of the pyridazine system, which were further oxidized by CAN toward different types of pyridazines.

2. Results and discussion

In the first stage we examined the preparation of 1,4-dihydropyridazines **2**, containing a fused polymethylene chain, by the reaction of fused pyran-2-ones **1** with hydrazine hydrate (Scheme 1). The reaction of cyclooctene-fused pyran-2-one **1b** with hydrazine hydrate, when using similar conditions to those that we preliminarily applied for the

Keywords: Heterocycles; Pyridazine-3-carbohydrazides; Esters; Dehydrogenation; Oxidation; Ammonium cerium(IV) nitrate.
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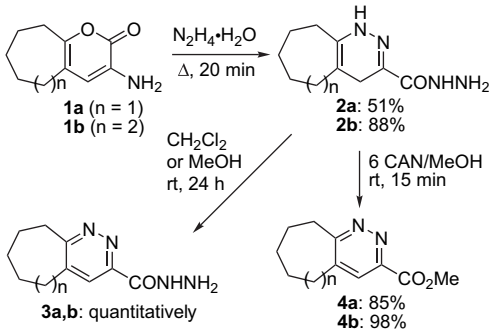
doi:10.1016/j.tet.2006.07.061

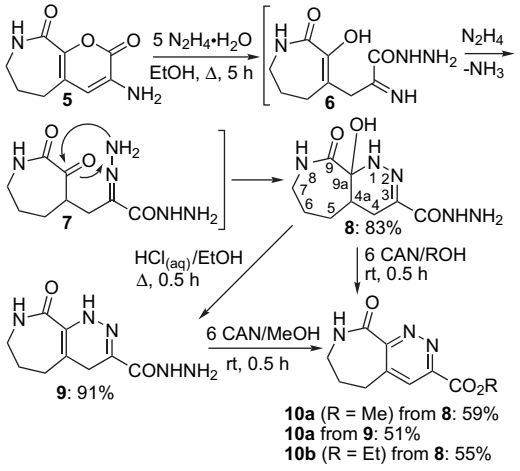
transformation of pyrano[3,2-*c*]azepines,[11e] was not complete after 9 h, as indicated by TLC. On the other hand, when the reactions of **1a**,**b** were carried out in boiling hydrazine hydrate, which served as the reagent and as a solvent, pure dihydropyridazine derivatives **2a**,**b** were isolated after a short reaction time (20 min) with good-to-excellent yields (up to 88%).



Scheme 1. Synthesis of cycloalkene-fused pyridazines.

^{1}H NMR spectra of **2a** and **2b** in DMSO-d_6 solutions revealed that these compounds have the 1,4-dihydropyridazine structure and no trace of any other tautomer was observed. In fact, a characteristic two-proton signal appeared at ~2.85 ppm (A_2 system) for methylene protons at position 4, whereas 1-H protons showed a resonance around 9 ppm. Compounds **2** are sensitive to oxidation from the air in solution, as well as in the crystalline form, and readily transformed into their aromatic analogues **3**. Thus, stirring of the compounds **2a**,**b** for 24 h in methylene chloride (or methanol) at room temperature in the presence of air afforded **3a**,**b** in a quantitative yield, whereas in the crystalline form after 24 h an ~90% aromatization of the compound **2b** took place. This transformation can be considerably reduced by storing compounds **2** in an argon atmosphere at low temperature. For example, with the compound **2b**, after three months at approximately −30 °C in a closed bottle under argon atmosphere only an approximately 5% conversion into **3b** was observed. It has been reported that dihydropyridazines are reactive toward molecular oxygen, normally forming the corresponding aromatic pyridazines;[12] however, in certain cases they gave hydroperoxides and endoperoxides.[12a] With our compounds, though, we were not able to detect or isolate any other intermediate: only pyridazine derivatives **3** were obtained as the final products. Additionally, we could accelerate the above dehydrogenation by bubbling oxygen into the refluxed mixture of **2b** in methanol; in this particular case the reaction was completed within 4 h to give **3b**. When bubbling oxygen in the presence of 50 mass % of activated carbon (DARCO® KB)[13] the reaction was finished in 3 h to give quantitatively **3b**. Compounds **2** can also be smoothly oxidized with CAN in a methanolic solution to give the pyridazine esters **4** in 85% (**4a**) and 98% (**4b**) yields. In the course of this reaction the formation of the ester from the hydrazide is accompanied by a concomitant aromatization of the 1,4-dihydropyridazine ring.

In contrast to our previous observation of the behavior of pyrano[3,2-*c*]azepines in a reaction with hydrazine hydrate,[11e] the reaction of the isomeric pyrano[2,3-*c*]azepine derivative **5** with 5 equiv of hydrazine hydrate in boiling ethanol led to the 9a-hydroxypyridazino[3,4-*c*]azepine derivative **8** with a high yield (Scheme 2).



Scheme 2. Pyrano[2,3-*c*]azepine **5** as a synthon for pyridazino[3,4-*c*]azepines.

The structure of the compound **8** was established on the basis of its NMR spectroscopic data. The two- and three-bond H, C connectivities, obtained from the HMBC measurement, strongly support the 9a-hydroxy-4,4a,5,6,7,8,9,9a-octahydro-1*H*-pyridazino[3,4-*c*]azepine structure; namely, 1-H, 8-H, the methylene protons at position 4 (4-CH_aH_b protons not being chemically and magnetically equivalent), and the hydroxy group correlate with 9a-C (78.7 ppm) in the HMBC spectrum, whereas the 1-H and 4-CH_aH_b protons correlate with 3-C (135.5 ppm), thus revealing an azepine-fused pyridazine skeleton and not an open-ring intermediate **7** (or its tautomer) (Fig. 1).

Compound **8** has been found to readily eliminate a water molecule when treated with aqueous HCl in absolute ethanol, thus giving the 4,5,6,7,8,9-hexahydro-1*H*-pyridazino[3,4-*c*]azepine derivative **9**. Treatment of the compound **8** with 6 equiv of CAN in an alcoholic solution led to the isolation of the fused pyridazine esters **10** in moderate yields (55–59%). Alternatively, the esters **10** can also be prepared by the oxidation of the compound **9** with CAN, as shown in

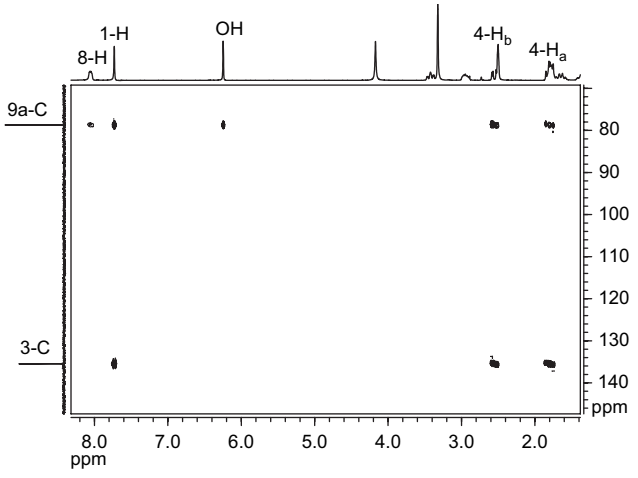
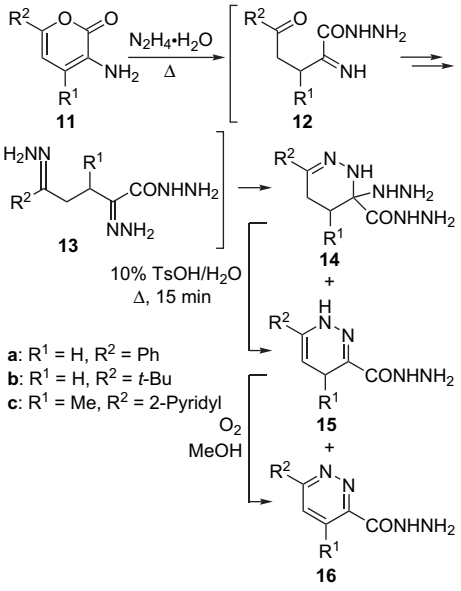


Figure 1. A part of the ^{1}H–^{13}C HMBC spectrum of the compound **8**.

the case of the methyl ester **10a**. On the basis of the above results we can assume that an acidic medium catalyzes the elimination of a water molecule from the compound **8** during the oxidation with CAN, thus initially giving the 1,4-dihydropyridazine intermediate, which is further dehydrogenated and transformed to the aromatic pyridazine esters **10** as the final products. The described method is very convenient for the preparation of pyridazino[3,4-*c*]azepines for which, to our knowledge, only two representatives have been previously described.[14]

Bearing in mind the above results of the fused pyran-2-ones, we decided to focus our attention on studies of the susceptibility of non-fused 2*H*-pyran-2-ones **11** to nucleophilic attack by a hydrazine molecule (Scheme 3, Table 1).



Scheme 3. Reaction of 2*H*-pyran-2-ones **11** with hydrazine.

Due to the absence of a fused ring in the compounds **11**, after the opening of the lactone ring with hydrazine the formation of a more flexible intermediate might be expected; this might then open up possibilities for different reactions. For example, one might expect that such an open-ring system would not be prone to cyclization, thus allowing an attack of additional hydrazine molecule(s). Indeed, when 6-substituted 2*H*-pyran-2-ones **11a** and **11b** were allowed to react with boiling hydrazine hydrate for 20 min the products **14a** and **14b** were isolated in 76 and 67% yields, respectively. The product **14b** was also accompanied by a small quantity (17%) of the 1,4-dihydropyridazine derivative **15b**. On the other hand, after refluxing the 2*H*-pyran-2-one **11c** in the presence of 5 equiv of hydrazine hydrate using ethanol or butanol as a solvent, we isolated the 1,4-dihydropyridazine derivative **15c**, which in ethanol was accompanied by the aromatic pyridazine **16c** (entries 3 and 4, Table 1). Compounds **14a**,**b** can easily eliminate a hydrazine molecule, when applying acidic conditions (10 mol % of TsOH in aqueous solution), to give **15a**,**b** in 90 and 71% yields, respectively. Compounds **15** have been found to be sensitive to the oxygen in air. For example, if **15b** was stirred in methylene chloride for 24 h at room temperature, a conversion into the aromatic pyridazine **16b** was observed in more than 95% (according to the ^{1}H NMR spectrum). On the other hand, 1,4-dihydropyridazine **15c** was found to be more resistant toward such oxidation in air; 72-h-stirring of its methanolic solution at room temperature resulted only in negligible formation of the aromatic analogue **16c** (as indicated by TLC). Aromatization was successfully accomplished by 7-h-bubbling of oxygen into the refluxed mixture of **15c** and 50 mass % of activated carbon (DARCO® KB) in methanol. For comparison, in the absence of activated carbon, but just bubbling oxygen into the refluxed mixture for 10 h, a conversion of about 40% of **15c** took place.

Table 1. Reaction of 2*H*-pyran-2-ones **11** with hydrazine

Entry	Starting **11**	*t*	Products (yield, %)[a]
1	**11a**	20 min[b]	**14a** (76)
2	**11b**	20 min[b]	**14b** (67)+**15b** (17)
3	**11c**	22 h[c]	**15c** (41)[d]+**16c** (7)[d]
4	**11c**	4.5 h[e]	**15c** (71)[d]

[a] Yields of isolated products are given.
[b] Hydrazine hydrate used as a solvent.
[c] Five equivalents of $N_2H_4 \cdot H_2O$ in ethanol.
[d] Yield after isolation by column chromatography.
[e] Five equivalents of $N_2H_4 \cdot H_2O$ in butanol.

The structures of the compounds **14** were determined on the basis of microanalyses, mass spectra, and NMR data. The mass spectra of the compounds **14a** and **14b** only showed peaks after the elimination of a hydrazine molecule ($MH^+ - N_2H_4$ or $M^+ - N_2H_4$), thus indicating that they contain in their structure a labile hydrazine moiety. In the HMBC spectrum of the compound **14a**, the *ortho* protons of the phenyl group and the 2-H correlate with the 6-C of the pyridazine ring, thus supporting the 2,3,4,5-tetrahydropyridazine structure (Fig. 2).

Additionally, it has been reported previously that the imine fragments of 2,3,4,5-tetrahydro-3-pyridazine carboxylic acid derivatives show characteristic signals at $\delta_C \approx$ 140 ppm.[15] This is in agreement with our observation for the compound **14a**, where the resonance signal for 6-C appears at 140.9 ppm. Furthermore, the 2-H as well as the methylene protons at positions 4 and 5 of the pyridazine

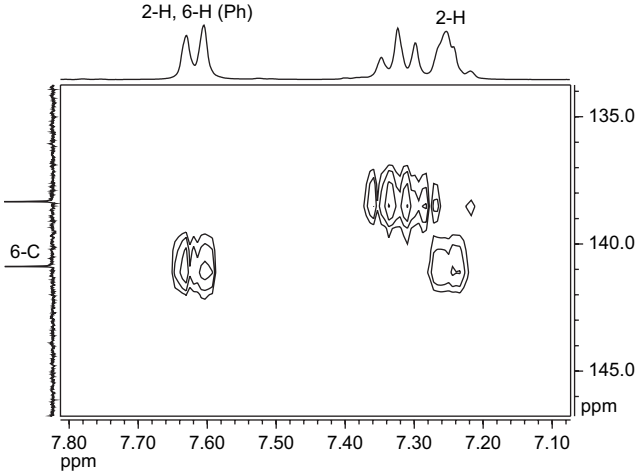


Figure 2. A part of the ^{1}H–^{13}C HMBC spectrum of the compound **14a**.

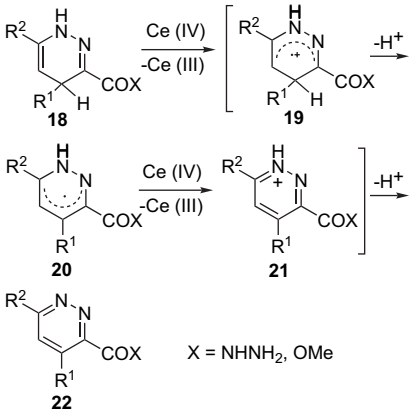
ring in compound **14a** correlate with the 3-C. This carbon atom shows a resonance at 71.9 ppm, which is consistent with the chemical shift of a quaternary sp^3 carbon atom deshielded by the neighboring heteroatoms.[16]

The formation of the products **14** and **15** from **11** might be explained as follows. We assume that after the opening of the lactone ring of the 2*H*-pyran-2-ones **11** with hydrazine, yielding the intermediate **12**, the attack of two additional hydrazine molecules at the electrophilic C=O and C=N groups of **12** takes place, thus leading to the α,δ-dihydrazonohydrazide derivative **13** as an intermediate. Furthermore, compounds **14** could be formed from **13** by the cyclization of the amino group of the δ-hydrazone moiety with the C=N group of α-hydrazone. After the elimination of a hydrazine molecule from **14** the dihydropyridazine **15** is finally formed in a 1,4-dihydro tautomeric form.

To demonstrate the utility of the compounds **14** and **15**, we treated them with 6–8 equiv of CAN in the presence of methanol and, after isolation by extraction, pyridazine-3-carboxylic esters **17a–c** were obtained as the sole products in a 79–93% yield (Table 2). It is obvious that an oxidation of the hydrazide function was accompanied by an acid-catalyzed elimination of hydrazine from compounds **14** (as mentioned above), and the dehydrogenation of a 1,4-dihydropyridazine ring.

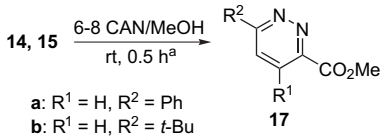
In all the above transformations with CAN a 1,4-dihydropyridazine ring was dehydrogenated in addition to the oxidation of the carbohydrazide moiety. The latter reaction toward the corresponding esters proceeds probably via acyl diimides as intermediates and eventually also via the formation of the acyl cation as discussed previously.[8]

On the other hand, to our knowledge, the oxidation of the 1,4-dihydropyridazine ring has not yet been rationalized. It seems reasonable to propose a tentative pathway related to those depicted for oxidations of 1,4-dihydropyridines.[17] Oxidation of a 1,4-dihydropyridazine **18** with CAN is presumably initiated by a single electron transfer to Ce(IV) generating a resonance stabilized radical cation **19** (Scheme 4), which then loses a proton to give a stabilized radical **20**. In the subsequent oxidation the protonated pyridazine **21** is produced and further transformed to the aromatized derivative **22**.



Scheme 4. Dehydrogenation of the 1,4-dihydropyridazine ring with Ce(IV).

Table 2. Oxidation of compounds **14** and **15** with CAN in the presence of methanol



a: R^1 = H, R^2 = Ph
b: R^1 = H, R^2 = *t*-Bu
c: R^1 = Me, R^2 = 2-Pyridyl

Entry	Starting **14** or **15**	Product (yield, %)[b]
1	**14a**	**17a** (93)[c]
2	**14b**	**17b** (89)[c]
3	**15b**	**17b** (84)[d]
4	**15c**	**17c** (79)[d]

[a] Reaction time after the addition of the entire amount of compound **14** or **15** to the mixture of CAN in methanol.
[b] Yields of isolated products are given.
[c] Eight equivalents of CAN used.
[d] Six equivalents of CAN used.

3. Conclusion

We have presented a new transformation of a variety of 2*H*-pyran-2-ones and fused pyran-2-ones with hydrazine hydrate into the corresponding 1,4-dihydropyridazine derivatives. We found that different pyran-2-ones required different reaction conditions for successful transformation to the pyridazine system. We have also shown that CAN is able to serve as a very useful oxidant for the carbohydrazide moiety as well as for the dehydrogenation of the 1,4-dihydropyridazine ring. Since it was previously shown that representatives of 2,3,4,5-tetrahydropyridazine-3-carboxylic acids and their derivatives possess a variety of biological activities,[2,15] the reported method and transformation might be of interest for the further design of similar novel compounds.

4. Experimental

4.1. General

Compounds **1** and **11** were prepared from 3-benzoylamino-substituted pyran-2-one derivatives by a known method.[18,19] Compound **5** was prepared as described in the literature.[11d] All other reagents and solvents were used as obtained from commercial suppliers. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 29 °C 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 and $CDCl_3$ at δ=77.0 ppm. TLC was carried out on silica-gel TLC cards. Column chromatography was carried out with silica-gel 60 (220–440 mesh).

4.2. General procedure for the preparation of pyridazines 2a,b, 14a,b, and 15b

A mixture of **1a**,**b**[18] or **11a**,**b**[18] (2 mmol) and hydrazine hydrate (1.5 g, 98%, 29.36 mmol) was refluxed for 20 min and then evaporated under reduced pressure. A mixture of water/methanol (5:1) (3 mL) in the case of **2a** or water (3 mL) in the case of **2b** was added to the residue. Upon cooling, the precipitated yellow solid was filtered off and washed with

a small amount of water to give **2a** (or **2b**). For **14a**,**b**, methanol (3 mL) was added to the residue, and upon cooling the white solid product **14a**,**b** was filtered off. After the separation of **14a** the filtrate was concentrated to 50% of its volume under reduced pressure to give an additional quantity of **14a**. The filtrate after the filtration of **14b** was evaporated to dryness, and diethyl ether (1.5 mL) was added to the residue. Upon cooling, a yellow solid **15b** was filtered off.

4.3. General procedure for the preparation of pyridazines 8, 15c, and 16c

A mixture of **5**[11d] or **11c**[18] (2 mmol), hydrazine hydrate (511 mg, 98%, 10 mmol), and absolute ethanol (8 mL) was refluxed for 5 h (for **8**) or for 22 h (for **15c**/**16c**). For the preparation of pure **15c** the solution of **11c** and hydrazine hydrate in butanol (8 mL) was refluxed for 4.5 h. The solvent was evaporated under reduced pressure. For **8**, methanol (4 mL) was added to the solid residue and, upon cooling, a white solid was filtered off and washed with a small amount of methanol. For the separation of the mixture **15c**/**16c** column chromatography (ethyl acetate/MeOH 25:1) of the solid residue was applied. For the isolation of pure **15c** (in the case where butanol was used as a solvent) column chromatography (ethyl acetate/MeOH 25:1) was applied.

4.4. Transformation of 8 to 9

A mixture of **8** (241 mg, 1 mmol), aqueous hydrochloric acid (200 mg, 9%), and absolute ethanol (5 mL) was refluxed for 0.5 h. The reaction mixture was evaporated, water (5 mL) was added to the residue and the mixture was neutralized with solid $NaHCO_3$. Upon cooling, the precipitate was filtered off and washed with water to give **9** (203 mg, 91%) as a yellow solid.

4.5. Transformation of 14 to 15

A mixture of **14a**,**b** (1 mmol), *p*-toluenesulfonic acid (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 **15a**,**b** as yellow solids. Yields: **15a** (194 mg, 90%), **15b** (139 mg, 71%).

4.6. Aromatization of 1,4-dihydropyridazine derivatives 2 and 15

A solution of **2** or **15b** (1 mmol) in MeOH or CH_2Cl_2 (4 mL) was stirred at room temperature in the presence of air for 24 h. The solvent was evaporated in vacuo to afford **3** in a quantitative yield. In the case of **15b**, over 95% conversion to **16b** occurred as indicated on the basis of ^{1}H NMR spectrum of the crude product. By bubbling oxygen into the refluxed mixture of **15c** (50 mg, 0.216 mmol) and activated charcoal DARCO® KB (Aldrich) (25 mg) in methanol (4 mL) for 7 h a complete conversion to **16c** was observed.

4.7. General procedure for the oxidation of the pyridazine derivatives 2, 8, 9, 14, and 15 with CAN

To a stirred mixture of CAN (6–8 mmol; see Schemes 1 and 2, and Table 2) in methanol (10–15 mL) at room temperature **2**, **8**, **9**, **14** or **15** (1 mmol) was added over a period of 10–20 min. The stirring was continued for 0.25–0.5 h, then the solvent was evaporated under reduced pressure, the solid residue was treated with water (10 mL), and the aqueous mixture was extracted with methylene chloride (6×10 mL). The collected organic layers were dried over anhydrous Na_2SO_4 and evaporated to give **4**, **10** or **17**. In the case of **4a**, further purification by column chromatography ($CHCl_3$/MeOH 25:1) was applied.

4.8. Analytical and spectroscopic data of products

4.8.1. 4,5,6,7,8,9-Hexahydro-1*H*-cyclohepta[*c*]pyridazine-3-carbohydrazide (2a). Mp 80–84 °C (MeOH/H_2O). IR (KBr): 3376, 2918, 1648, 1608, 1504 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.47 (m, 4H), 1.63 (m, 2H), 1.99 (m, 2H), 2.12 (m, 2H), 2.86 (s, 2H), 4.20 (s, 2H), 8.74 (s, 1H), 8.96 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 25.5, 26.3, 26.9, 28.9, 30.8, 32.3, 103.0, 131.6, 135.5, 164.5. EI-MS: *m*/*z* (%) 208 (M$^+$, 15), 192 (100). Anal. Calcd for $C_{10}H_{16}N_4O$: C, 57.67; H, 7.74; N, 26.90. Found: C, 57.69; H, 8.01; N, 27.25.

4.8.2. 1,4,5,6,7,8,9,10-Octahydrocycloocta[*c*]pyridazine-3-carbohydrazide (2b). Mp 93–94 °C (MeOH/H_2O). IR (KBr): 3356, 2920, 2849, 1626, 1497 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.44 (m, 8H), 2.03 (m, 2H), 2.15 (m, 2H), 2.83 (s, 2H), 4.20 (s, 2H), 8.74 (s, 1H), 9.04 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 24.3, 25.8, 25.9, 26.0, 27.2, 28.9, 29.1, 100.6, 131.4, 133.0, 164.6. EI-MS: *m*/*z* (%) 222 (M$^+$, 15), 206 (100). Anal. Calcd for $C_{11}H_{18}N_4O$: C, 59.44; H, 8.16; N, 25.20. Found: C, 59.64; H, 8.34; N, 25.50.

4.8.3. 6,7,8,9-Tetrahydro-5*H*-cyclohepta[*c*]pyridazine-3-carbohydrazide (3a). Mp 172.8–173.4 °C (EtOAc). IR (KBr): 3307, 3256, 3206, 2935, 2923, 2854, 1682, 1668, 1632, 1585, 1501 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.63 (m, 4H), 1.84 (m, 2H), 2.90 (m, 2H), 3.24 (m, 2H), 4.64 (s, 2H), 7.88 (s, 1H), 10.23 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 25.9, 26.7, 31.3, 33.4, 35.8, 124.4, 143.8, 151.7, 161.7, 166.7. EI-MS: *m*/*z* (%) 206 (M$^+$, 99.5), 148 (100). Anal. Calcd for $C_{10}H_{14}N_4O$: C, 58.24; H, 6.84; N, 27.16. Found: C, 58.54; H, 7.00; N, 26.89.

4.8.4. 5,6,7,8,9,10-Hexahydrocycloocta[*c*]pyridazine-3-carbohydrazide (3b). Mp 168–171 °C (EtOAc). IR (KBr): 3310, 3248, 3202, 2931, 2858, 1679, 1631, 1505 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.31 (m, 4H), 1.73 (m, 4H), 2.87 (m, 2H), 3.16 (m, 2H), 4.69 (br s, 2H), 7.91 (s, 1H), 10.22 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 25.1, 25.2, 30.0, 30.5, 30.9, 31.6, 124.7, 142.1, 151.6, 161.7, 165.3. EI-MS: *m*/*z* (%) 220 (M$^+$, 100). Anal. Calcd for $C_{11}H_{16}N_4O$: C, 59.98; H, 7.32; N, 25.44. Found: C, 59.94; H, 7.56; N, 25.60.

4.8.5. Methyl 6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridazine-3-carboxylate (4a). Mp 58.5–59.2 °C (Et_2O). IR (KBr): 3045, 2920, 2848, 1729 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.65 (m, 4H), 1.86 (m, 2H), 2.90 (m, 2H), 3.26 (m, 2H), 3.94 (s, 3H), 7.97 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 25.8, 26.5, 31.3, 33.2, 35.9, 52.6, 126.7, 143.4, 150.0, 164.5, 167.5. EI-MS: *m*/*z* (%)

206 (M^+, 18), 148 (100). Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.31; H, 7.01; N, 13.41.

4.8.6. Methyl 5,6,7,8,9,10-hexahydrocycloocta[*c*]pyridazine-3-carboxylate (4b). Mp 60–62 °C (Et_2O). IR (KBr): 2940, 2911, 2859, 1715 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.31 (m, 4H), 1.73 (m, 4H), 2.87 (m, 2H), 3.19 (m, 2H), 3.94 (s, 3H), 8.00 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 25.0, 25.2, 29.8, 30.4, 30.8, 31.7, 52.6, 127.1, 141.7, 149.8, 164.5, 166.1. EI-MS: *m*/*z* (%) 220 (M^+, 30), 162 (100). Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.18; H, 7.53; N, 13.01.

4.8.7. 9a-Hydroxy-9-oxo-4,4a,5,6,7,8,9,9a-octahydro-1*H*-pyridazino[3,4-*c*]azepine-3-carbohydrazide (8). Mp 166–169 °C (MeOH/DMF). IR (KBr): 3318 br, 1678, 1656, 1616, 1507 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.24 (m, 1H), 1.38 (m, 1H), 1.64 (m, 1H), 1.79 (m, 3H), 2.56 (dd, J=17.3, 4.7 Hz, 1H), 2.95 (m, 1H), 3.42 (m, 1H), 4.16 (br s, 2H), 6.24 (s, 1H), 7.72 (s, 1H), 8.05 (dd, J=ca. 3.7 and 7.6 Hz, 1H), 8.77 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 24.3, 28.9, 31.4, 31.9, 41.0, 78.7, 135.5, 163.9, 172.7. EI-MS: *m*/*z* (%) 241 (M^+, 30), 163 (100). Anal. Calcd for $C_9H_{15}N_5O$: C, 44.81; H, 6.37; N, 29.03. Found: C, 45.06; H, 6.43; N, 29.32.

4.8.8. 9-Oxo-4,5,6,7,8,9-hexahydro-1*H*-pyridazino[3,4-*c*]azepine-3-carbohydrazide (9). Mp 196–198 °C (MeOH/DMF). IR (KBr): 3392, 3333, 3317, 3291, 3212, 1659, 1640 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.82 (m, 2H), 2.34 (m, 2H), 2.90 (s, 2H), 3.09 (m, 2H), 4.27 (s, 2H), 8.15 (dd, $J_1 \approx J_2 \approx 5.0$ Hz, 1H), 8.92 (s, 1H), 9.02 (br s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 27.1, 27.7, 33.1, 40.2, 113.6, 127.5, 132.5, 163.2, 164.2. EI-MS: *m*/*z* (%) 223 (M^+, 29), 163 (100). Anal. Calcd for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.37. Found: C, 48.42; H, 6.16; N, 31.66.

4.8.9. Methyl 9-oxo-6,7,8,9-tetrahydro-5*H*-pyridazino[3,4-*c*]azepine-3-carboxylate (10a). Mp 206–208 °C (EtOH). IR (KBr): 3196, 3075, 1742, 1665, 1584 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.93 (m, 2H), 2.92 (m, 4H), 3.98 (s, 3H), 8.24 (s, 1H), 8.63 (dd, $J_1 \approx J_2 \approx 5.7$ Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 27.0, 28.3, 37.4, 53.0, 127.9, 138.9, 151.4, 158.3, 164.0, 166.5. EI-MS: *m*/*z* (%): 221 (M^+, 27), 163 (100). Anal. Calcd for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.36; H, 5.18; N, 19.16.

4.8.10. Ethyl 9-oxo-6,7,8,9-tetrahydro-5*H*-pyridazino[3,4-*c*]azepine-3-carboxylate (10b). Mp 210–212 °C (EtOH). IR (KBr): 3200, 3090, 2931, 1720, 1668 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.39 (t, J=7.1 Hz, 3H), 1.95 (m, 2H), 2.93 (m, 4H), 4.46 (q, J=7.1 Hz, 2H), 8.23 (s, 1H), 8.64 (dd, $J_1 \approx J_2 \approx 5.9$ Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 14.0, 27.0, 28.3, 37.5, 61.9, 127.8, 138.9, 151.5, 158.3, 163.5, 166.5. EI-MS: *m*/*z* (%) 235 (M^+, 4), 163 (100). Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.03; H, 5.74; N, 17.94.

4.8.11. 3-Hydrazino-6-phenyl-2,3,4,5-tetrahydropyridazine-3-carbohydrazide (14a). Mp 108–111 °C (pyridine). IR (KBr): 3306, 3264, 3164, 1667, 1603, 1498 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.90 (m, 2H), 2.50 (m, 2H), 3.31 (br s, 2H), 4.10 (br s, 1H), 4.26 (br s, 2H), 7.29 (m, 4H), 7.62 (m, 2H), 9.03 (br s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 19.5, 24.9, 71.9, 123.9, 127.2, 128.0, 138.3, 140.9, 171.2. FABMS: *m*/*z* (%) 217 ($MH^+-N_2H_4$, 52), 185 (100). HRMS (EI) calcd for $C_{11}H_{12}N_4O$ ($M^+-N_2H_4$) 216.1011, found 216.1017. Anal. Calcd for $C_{11}H_{16}N_6O$: C, 53.21; H, 6.50; N, 33.85. Found: C, 53.49; H, 6.68; N, 33.54.

4.8.12. 6-*tert*-Butyl-3-hydrazino-2,3,4,5-tetrahydropyridazine-3-carbohydrazide (14b). Mp 108–109 °C (pyridine). IR (KBr): 3305, 3267, 3170, 2962, 1666, 1608, 1507 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.02 (s, 9H), 1.67 (m, 2H), 2.07 (m, 2H), 3.20 (br s, 2H), 3.93 (br s, 1H), 4.21 (br s, 2H), 6.44 (s, 1H), 8.91 (br s, 1H). FABMS: *m*/*z* (%) 197 ($MH^+-N_2H_4$). HRMS (EI) calcd for $C_9H_{16}N_4O$ ($M^+-N_2H_4$) 196.1324, found 196.1330. Anal. Calcd for $C_9H_{20}N_6O$: C, 47.35; H, 8.83; N, 36.81. Found: C, 47.09; H, 8.83; N, 37.10.

4.8.13. 6-Phenyl-1,4-dihydropyridazine-3-carbohydrazide (15a). Mp 162–164 °C (EtOAc/MeOH). IR (KBr): 3368, 3318, 3203, 1670, 1653, 1628, 1506 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.06 (d, J=3.9 Hz, 2H), 4.31 (s, 2H), 4.89 (dt, J=2.3, 3.9 Hz, 1H), 7.38 (m, 3H), 7.50 (m, 2H), 8.93 (s, 1H), 9.75 (d, J=2.3 Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 21.1, 92.0, 125.3, 128.3, 128.4, 132.8, 133.8, 138.5, 164.0. EI-MS: *m*/*z* (%) 216 (M^+, 26), 200 (100). Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.09; H, 5.79; N, 25.62.

4.8.14. 6-*tert*-Butyl-1,4-dihydropyridazine-3-carbohydrazide (15b). Mp 144–146.5 °C (EtOAc/light petroleum). IR (KBr): 3391, 3372, 3304, 3274, 3205, 2961, 1672, 1621, 1499 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.07 (s, 9H), 2.85 (d, J=3.6 Hz, 2H), 4.24 (br s, 2H), 4.30 (dt, J=2.6, 3.6 Hz, 1H), 8.72 (s, 1H), 9.17 (d, J=2.6 Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 20.6, 27.9, 32.6, 87.0, 132.0, 147.0, 164.2. EI-MS: *m*/*z* (%) 196 (M^+, 33), 180 (100). Anal. Calcd for $C_9H_{16}N_4O$: C, 55.08; H, 8.22; N, 28.55. Found: C, 54.95; H, 8.45; N, 28.80.

4.8.15. 4-Methyl-6-(pyridin-2-yl)-1,4-dihydropyridazine-3-carbohydrazide (15c). Mp 130–132.5 °C (EtOAc/light petroleum). IR (KBr): 3385, 3314, 3202, 1660, 1634, 1594 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.96 (d, J=6.5 Hz, 3H), 3.60 (dq, J=6.5, 6.5 Hz, 1H), 4.32 (s, 2H), 5.71 (dd, J=2.2, 6.5 Hz, 1H), 7.37 (ddd, J=1.4, 4.9, 7.0 Hz, 1H), 7.80 (ddd, J=1.4, 1.4, 7.6 Hz, 1H), 7.85 (ddd, J=1.8, 7.0, 7.6 Hz, 1H), 8.57 (ddd, J=1.4, 1.8, 4.9 Hz, 1H), 9.00 (s, 1H), 9.71 (d, J=2.2 Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 19.5, 24.8, 100.4, 119.1, 123.3, 135.8, 137.1, 137.2, 148.4, 149.8, 163.5. EI-MS: *m*/*z* (%) 231 (M^+, 36), 216 (100). Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 57.20; H, 5.69; N, 29.91.

4.8.16. 6-*tert*-Butylpyridazine-3-carbohydrazide (16b). Mp 109–111 °C (Et_2O). IR (KBr): 3387, 3325, 2962, 1671, 1601, 1515 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.42 (s, 9H), 4.68 (br s, 2H), 7.96 (d, J=8.9 Hz, 1H),

8.08 (d, J=8.9 Hz, 1H), 10.30 (br s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 29.6, 36.9, 124.7, 125.3, 151.1, 161.6, 171.2. EI-MS: m/z (%) 194 (M^+, 100). Anal. Calcd for $C_9H_{14}N_4O$: C, 55.65; H, 7.27; N, 28.85. Found: C, 55.83; H, 7.42; N, 28.85.

4.8.17. 4-Methyl-6-(pyridin-2-yl)pyridazine-3-carbohydrazide (16c). Mp 177.5–180 °C (MeOH). IR (KBr): 3314 br, 1661, 1626, 1580, 1503 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.56 (d, J=1 Hz, 3H), 4.69 (s, 2H), 7.59 (ddd, J=1.1, 4.8, 7.7 Hz, 1H), 8.05 (ddd, J=1.8, 7.7, 7.9 Hz, 1H), 8.47 (q, J=1 Hz, 1H), 8.57 (ddd, J=1.1, 1.1, 7.9 Hz, 1H), 8.78 (ddd, J=1.1, 1.8, 4.8 Hz, 1H), 10.06 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 18.1, 121.3, 125.3, 126.2, 137.7, 138.1, 149.7, 152.4, 154.9, 157.7, 163.8. EI-MS: m/z (%) 229 (M^+, 100). Anal. Calcd for $C_{11}H_{11}N_5O$: C, 57.63; H, 4.84; N, 30.55. Found: C, 57.91; H, 5.04; N, 30.24.

4.8.18. Methyl 6-phenylpyridazine-3-carboxylate (17a). Mp 194–197 °C (MeOH/H_2O). IR (KBr): 3062, 2952, 1717, 1575, 1442, 1409 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.10 (s, 3H), 7.56 (m, 3H), 8.00 (d, J=8.9 Hz, 1H), 8.17 (m, 2H), 8.24 (d, J=8.9 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 53.2, 123.9, 127.6, 128.0, 129.2, 130.9, 135.4, 150.0, 160.7, 164.7. EI-MS: m/z (%) 214 (M^+, 45), 156 (100). Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.15; H, 4.84; N, 12.88.

4.8.19. Methyl 6-*tert*-butylpyridazine-3-carboxylate (17b). Mp 115–116.5 °C (MeOH/H_2O). IR (KBr): 2963, 1721, 1576, 1448, 1359, 1298 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.42 (s, 9H), 3.97 (s, 3H), 7.98 (d, J=8.9 Hz, 1H), 8.14 (d, J=8.9 Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 29.5, 37.0, 52.7, 124.3, 127.7, 149.4, 164.3, 171.9. EI-MS: m/z (%) 194 (M^+, 15), 152 (100). HRMS calcd for $C_{10}H_{14}N_2O_2$ 194.1055, found 194.1060. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.56; H, 7.39; N, 14.85.

4.8.20. Methyl 4-methyl-6-(pyridin-2-yl)pyridazine-3-carboxylate (17c). Mp 106.5–108 °C (EtOAc/light petroleum). IR (KBr): 1719, 1579, 1441, 1379 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.58 (d, J=0.8 Hz, 3H), 3.99 (s, 3H), 7.60 (ddd, J=1.1, 4.8, 7.7 Hz, 1H), 8.07 (ddd, J=1.8, 7.7, 7.9 Hz, 1H), 8.53 (q, J=ca. 0.8 Hz, 1H), 8.60 (ddd, J=1.1, 1.1, 7.9 Hz, 1H), 8.79 (ddd, J=1.1, 1.8, 4.8 Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 18.5, 52.7, 121.6, 125.5, 126.3, 137.7, 139.2, 149.8, 152.0, 152.5, 158.1, 165.2. EI-MS: m/z (%) 229 (M^+, 35), 171 (100). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.66; H, 5.02; N, 18.25.

Acknowledgements

We thank the Ministry of Higher Education, Science, and Technology of the Republic of Slovenia as well as the Slovenian Research Agency for financial support (P1-0230-0103). Dr. B. Kralj and Dr. D. Žigon (Center for Mass Spectroscopy, 'Jožef Stefan' Institute, Ljubljana, Slovenia) are gratefully acknowledged for mass measurements.

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18. Starting compounds **1a** and **1b** were prepared from the corresponding ketones (cycloheptanone and cyclooctanone), *N*,*N*-dimethylformamide dimethyl acetal, and hippuric acid by a modification of the method described in Ref. 19a, followed by the removal of the benzoylamino group using the method described in Ref. 19b. 3-Amino-2*H*-pyran-2-ones **11** were prepared from previously known 3-benzoylamino-2*H*-pyran-2-ones by the known method.[19b]
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