A New Transformation of 2*H*-Pyran-2-one ring: First Synthesis of Pyridazino[4,3-*c*]azepines and their Oxidation with Thallium(III) Nitrate or Copper(II) Acetate[1]

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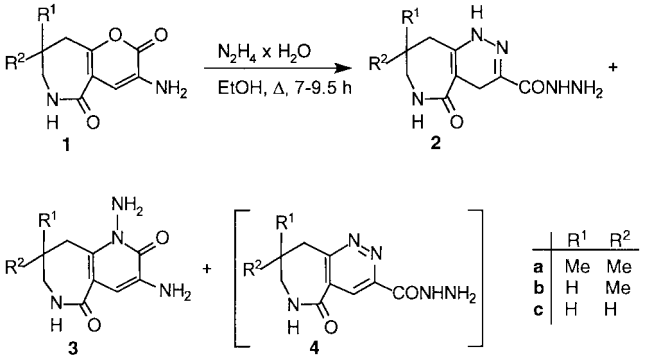
Abstract: A novel reaction starting from pyrano[3,2-*c*]azepines **1** and hydrazine hydrate was used for the preparation of the first derivatives of pyridazino[4,3-*c*]azepines **2**. They were further oxidised by thallium(III) nitrate trihydrate (TTN) or copper(II) acetate hydrate (CuDA) to give aromatised fused pyridazine derivatives **5** also containing an ester function formed from the carbohydrazide moiety.

Keywords: oxidation, esters, thallium(III) nitrate, copper(II) acetate, heterocycles, pyridazino[4,3-*c*]azepines

2*H*-Pyran-2-ones and fused pyran-2-ones are important synthons and building blocks in organic synthesis.[3] 2*H*-Pyran-2-ones are known to react with nitrogen containing nucleophiles that either attack at a side chain or open the pyran-2-one ring. The opened ring may then cyclise again to form pyridin-2(1*H*)-ones, pyrazoles or other rings. Synthesis of pyridazine derivatives[4] from 2- or 6-hydroxy-2*H*-pyran-2-ones was achieved decades ago by coupling pyran-2-one derivatives with aryldiazonium salts followed by further rearrangement of the intermediary formed hydrazones.[5] Similar conversions were also observed with some fused pyran-2-ones.[6] However, hydrazine and its derivatives normally do not convert pyran-2-ones into pyridazines; the corresponding pyridines or pyrazoles are formed instead.[7]

We report here a mechanistically new conversion of fused pyran-2-one derivatives into fused pyridazines and their further oxidation with TTN and CuDA. Initially, we studied the reaction of 3-aminopyrano[3,2-*c*]azepine **1a**[7a,8] with hydrazine hydrate (Scheme 1). After heating an equimolar reaction mixture of compounds **1a** and hydrazine hydrate in ethanol for 9 h, the mixture was evaporated in vacuo to dryness; the residue was washed with a small amount of diethyl ether and analysed by ^{1}H NMR. The product distribution is given in the Table (run 1). The main product in the reaction mixture, 1,4,6,7,8,9-hexahydro-8,8-dimethyl-5-oxo-5*H*-pyridazino[4,3-*c*]azepine-3-carboxylic acid hydrazide (**2a**), is the representative of a novel heterocyclic system. However, 1,3-diaminopyrido[3,2-*c*]azepine-2,5-dione **3a** is the expected[7a–b] product in this reaction. Aromatised fused pyridazine **4a**, which is obviously an oxidation product of **2a** by air, was not isolated in the pure state; its structure was determined on the basis of a ^{1}H NMR spectrum of the mixture. Since the formation of the product **2a** was unexpected and represented a new reaction with 2*H*-pyran-2-one derivatives, we focused our attention on its synthesis. From the Table it is evident that product **2a** can be prepared with relatively good yields and formation of the products **3a** and especially **4a** can be reduced to a very large extent. The best conditions for the synthesis of **2a** is heating a mixture of **1a** and a 2 molar amount of hydrazine hydrate in the presence of a catalytic amount of *p*-toluenesulfonic acid in ethanol (run 6); under basic conditions the formation of the product **3a** is favoured. These reaction conditions (run 6) were used for the synthesis of two additional representatives (**2b**–**c**) of pyridazino[4,3-*c*]azepines, which were prepared from **1b**–**c**[9] and hydrazine hydrate and isolated from the reaction mixture as TLC-pure products in 53 and 65% yields, respectively.[10,11] In these particular cases we did not try to isolate eventual by-products.



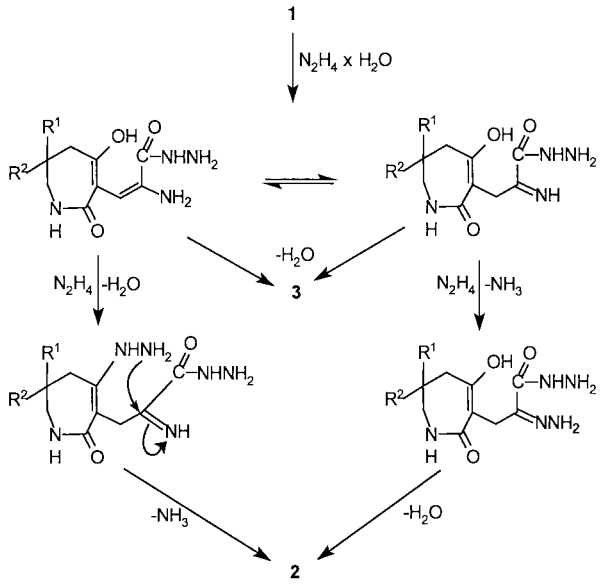
Scheme 1

Table Reaction conditions and distribution of products obtained from **1a** and $N_2H_4{\times}H_2O$

Run	1a (mmol)	$N_2H_4{\times}H_2O$ (mmol)	Solvent (mL); React. time (h)	Product distr. (%) 2a	1a	3a	4a
1	2.40	2.52	EtOH (9.6); 9	46	45	6	3
2	2.40	4.80	EtOH (9.6); 7.5	61	13	21	5
3	0.60	1.25	EtOH+Et_3N 4 : 1 (5); 5	54	0	32	14
4	5.00	10.45	Et_3N (20); 7	32	0	68	0
5	2.40	5.02	BuOH (20); 7	75	10	10	5
6	0.60	1.25	EtOH[a] (5); 10	79	9	5	7

[a]*p*-Toluenesulfonic acid hydrate (11.4 mg, 0.060 mmol) was added.

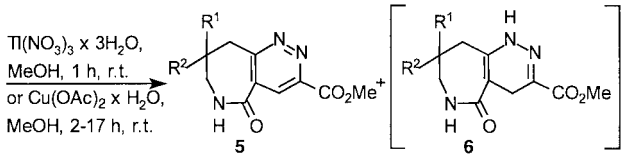
The formation of products **2** and **3** can be explained as outlined in Scheme 2. In contrast with our previous observation in the 2*H*-pyran-2-one series,[7c] nucleophilic attack of a hydrazine molecule that occurs at the lactone carbonyl group yields an open-ring intermediate, which is then cyclised by the action of the second molecule of hydrazine and the elimination of water and ammonia to give **2**. Products **3** could be formed by the cyclisation with the elimination of water from the first tautomeric intermediate.



Scheme 2

In order to obtain additional information concerning the above mechanism, reaction of **1a** with phenylhydrazine was performed. Unfortunately, after heating **1a** with 2 equivalents of phenylhydrazine in an ethanolic solution in the presence of *p*-toluenesulfonic acid for 20 h, followed by adding a new portion of phenylhydrazine (2 equivalents) and heating for an additional 20 h, we isolated 40% of the starting compound **1a**. When the 3-amino group in **1** was protected by a benzoyl group, a derivative of 1-aminopyrido[3,2-*c*]azepine **3** was obtained with hydrazine in an ethanolic solution.[7a] These results show that transformation to the fused pyridazines is very selective and requires a free amino group at the position 3 in the starting pyran-2-one derivative.

Recently, we have used TTN as an oxidant[12a,b] for the cleavage of the hydrazino moiety.[12c] We wanted to check its selectivity as an oxidising agent on compounds **2**, which contain two oxidizable moieties, namely, a 1,4-dihydropyridazine ring and a carbohydrazido group. In a preliminary experiment, we stirred (for 2.5 h) a mixture of **2a** (0.68 mmol) and TTN (1.02 mmol) in methanol. After work-up and separation of the products, the product **5a** was isolated with a 12% yield and its dihydro derivative **6a** with a 15% yield. Having obtained this result, we focused our attention on the synthesis of products **5** only. With a 3.5 molar quantity of TTN we isolated products **5a**–**c** with a 60–72% yield.[10,11]



	R^1	R^2	Yields with TTN	Yields with CuDA;[a] react. time
a	Me	Me	**5a** (72%)	**5a** (29%), **6a** (21%); 135 min
b	H	Me	**5b** (60%)	**5b** (38%), **6b** (13%); 17 h
c	H	H	**5c** (62%)	**5c** (37%), **6c** (24%); 7.5 h

[a]Yields without optimisation after separation by column chromatography.

Scheme 3

Since **thallium and its compounds are very toxic**,[12c] we decided to try to perform this reaction with other less dangerous oxidants. It has recently been reported that CuDA[12a] could be used for the cleavage of hydrazides, though in methanol it gave mainly free carboxylic acids, and methyl esters were obtained only as the minor products.[13] We successfully carried out the transformation of the hydrazino moiety into an ester and also partial aromatisation of the pyridazine ring with a 7-molar amount of CuDA in a very large volume of methanol (to avoid formation of carboxylic acids) and at room temperature. Mixtures of products **5** (main) and **6** were isolated and separated by column chromatography (Scheme 3). The longer the reactions continued, the higher the yields of aromatised products **5** attained with each substrate.

Further broad investigations of all the described conversions, including attempts with other pyran-2-one ring containing compounds as well as oxidation with a variety of oxidants,[14] are in progress.

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References and Notes

(1) Parts of this work have been presented at the 7th Blue Danube Symposium on Heterocyclic Chemistry, June 7–10, 1998, Eger, Hungary (Abstract PO56) and at the conference Slovenski kemijski dnevi (Slovene Chemistry Days), Maribor, Slovenia, September 17–18, 1998 (Zbornik referatov s posvetovanja, p 232).
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(9) Compounds **1b** and **1c** were prepared from 3-amino-7,8-dihydro-2*H*-1-benzopyran-2,5(6*H*)-dione and its 7-methyl analog[8] with hydrazoic acid by the known[7a] method.
(10) General procedure for the synthesis of pyridazino[4,3-*c*]azepine-3-carboxylic acid hydrazides **2a**–**c**: A mixture of compound **1** (1 mmol), 98% hydrazine hydrate (2.2 mmol) and *p*-toluenesulfonic acid hydrate (0.1 mmol) in absolute ethanol (4–8 mL) was refluxed for 7–9.5 h. After cooling, the yellow crystalline substance was filtered off to give TLC-pure **2b–c.** Additional amounts of products can be obtained by evaporation of the filtrate to dryness and addition of a small amount of absolute ethanol and cooling. For isolation of **2a** the reaction mixture was evaporated and the remaining residue was crystallised from BuOH/MeCN. Total yields 52–65%.
Typical procedure for the synthesis of **5** with TTN: To the stirred solution of **2a** (222 mg, 1 mmol) in methanol (12 mL), a solution of TTN (1.555 g, 3.5 mmol) in methanol (7 mL) was added, then it was diluted with an additional amount of methanol (5 mL) and stirred for 1 h. The solid was filtered off and washed with methanol (7 mL), the filtrate was evaporated in vacuo, the residue was diluted with water (30 mL) and extracted several times with chloroform to give 179 mg (72%) of TLC-pure product **5a** (without optimisation).
(11) New compounds gave satisfactory elemental analyses and were also identified on the basis of their NMR (DMSO-d_6, 300 MHz, for **6a** 60 MHz), IR and mass spectra. Selected data:
2a: mp (uncorrected) 202–205 °C (BuOH/MeCN); ^{1}H NMR δ 0.89 (6H, s, two Me), 2.03 (2H, s, 9-CH_2), 2.68 (2H, d, J = 5.45 Hz, 7-CH_2), 2.96 (2H, s, 4-CH_2), 4.29 (2H, br s, NH_2), 7.49 (1H, t, J = 5.45 Hz, 6-H), 9.07 (1H, br s, NH), 9.91 (1H, br s, NH).
2b: mp 243–245 °C, decomp (DMF/MeOH); ^{1}H NMR δ 0.86 (3H, d, J = 6.65 Hz, Me), 1.99 (1H, m, 9-H_a), 2.15 (1H, m, 8-H), 2.42 (1H, m, 9H_b), 2.64 (1H, m, 7-H_a), 2.96 (2H, s, 4-CH_2), 3.06 (1H, m, 7-H_b), 4.29 (2H, br s, NH_2), 7.40 (1H, deg t, 6-H), 9.07 (1H, br s, NH), 9.87 (1H, br s, NH).
2c: mp 227–229 °C (DMF); ^{1}H NMR δ 1.80 (2H, m, 8-CH_2), 2.36 (2H, m, 9-CH_2), 2.96 (2H, s, 4-CH_2), 3.01 (2H, m, 7-CH_2), 4.31 (2H, br s, NH_2), 7.39 (1H, t, J = 5.5 Hz, 6-H), 9.08 (1H, br s, NH), 9.84 (1H, br s, NH).
5a: mp 140–143 °C (Et_2O/hexane); ^{1}H NMR δ 1.01 (6H, s, two Me), 2.64 (2H, d, J = 6.0 Hz, 7-CH_2), 2.95 (2H, s, 9-CH_2), 3.98 (3H, s, OMe), 8.13 (1H, s, 4-H), 8.82 (1H, deg t, 6-H).
5b: mp 143–145 °C (Et_2O); ^{1}H NMR δ 0.98 (3H, d, J = 6.7 Hz, 8-Me), 2.46 (1H, m, 8-H), 2.62 (1H, m, 7-H_a), 2.86 (1H, m, 9-H_a), 3.07 (1H, m, 7-H_b), 3.33 (1H, m, 9-H_b), 3.98 (3H, s, OMe), 8.13 (1H, s, 4-H), 8.70 (1H, t, J = 5.5 Hz, 6-H).
5c: mp 221–224 °C (MeOH); ^{1}H NMR δ 2.09 (2H, m, 8-CH_2), 3.01 (2H, m, 7-CH_2), 3.23 (2H, m, 9-CH_2), 3.98 (3H, m, OMe), 8.13 (1H, s, 4-H), 8.64 (1H, deg t, 6-H).
6a:^{1}H NMR δ 0.90 (6H, s, two Me), 2.09 (2H, s, 9-CH_2), 2.76 (2H, d, J = 6 Hz, 7-CH_2), 3.07 (2H, s, 4-CH_2), 3.77 (3H, s, OMe), 7.65 (1H, t, J = 6 Hz, 6-H), 10.35 (1H, br s, NH); MS m/z 251 (M^+, 31%), 191 (100).
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