Base-Promoted Ring Contraction of Dihydrodiazepinones to Pyrrolinones

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Abstract

A novel synthesis of 2,3-dihydro-1*H*-1,3-diazepin-2-ones based on thermal elimination of methanol from 4-methoxy-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones has been developed. The prepared dihydrodiazepinones underwent a new rearrangement under basic conditions to give 3-(aminomethylene)-2,3-dihydro-1*H*-pyrrol-2-ones. Plausible mechanism for the rearrangement is proposed.

Keywords

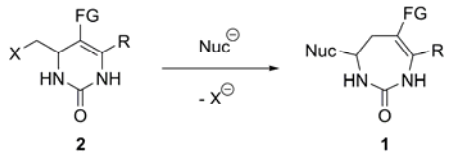
1*H*-1,3-Diazepin-2-ones; Ring contraction; 2,3-dihydro-1*H*-pyrrol-2-ones; Anti-aromaticity

Introduction

The development of general approaches to rare heterocyclic scaffolds and studies of their structure and reactivity is important from the viewpoint of synthetic, theoretical and medicinal chemistry. These scaffolds are represented by monocyclic 1,3-diazepines and their partly hydrogenated derivatives.[1] General strategies for their synthesis include various ring expansion reactions.[2-4] For example, photolysis of 2-azidopyridines or their bicyclic isomers, tetrazolo[1,5-*a*]pyridines, in the presence of water, alcohols or secondary amines gives access to 2,3-dihydro-1*H*-1,3-diazepin-2-ones, 2-alkoxy- and 2-dialkylamino-1*H*-1,3-diazepines, respectively.[4] The drawbacks of these methods are the poor availability of the starting compounds, limited possibilities for diversification, multistep syntheses, small-scale preparations, harsh reaction conditions, poor yields, etc. Therefore, the chemistry of these compounds remains under-explored. The only reactions described are their photochemical transformations into 2,4-diazabicyclo[3.2.0]heptane[4e,g] and pyrrole[4g,f] derivatives. Here we report a new and convenient synthesis of 5-functionalized 2,3-dihydro-1*H*-1,3-diazepin-2-ones and their rearrangements into 3-(aminomethylene)-2,3-dihydro-1*H*-pyrrol-2-ones or 1-carbamoyl-1*H*-pyrroles promoted by bases or acids, respectively.

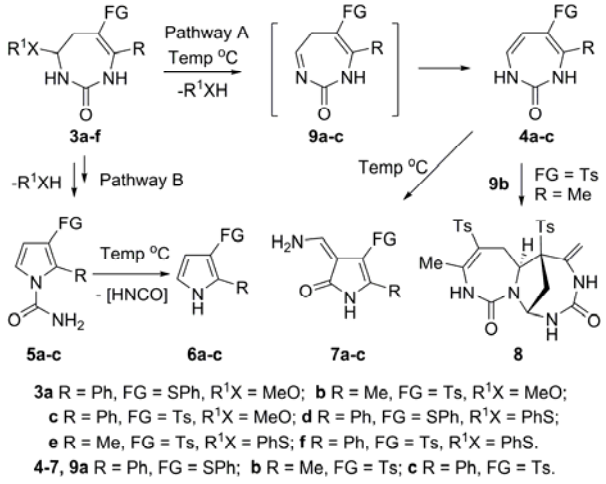
Results and discussion

We previously developed a general five-step synthesis of 6-functionalized 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones **1** based on the ring expansion of 1,2,3,4-tetrahydropyrimidin-2-ones **2** mediated by nucleophiles (Scheme 1).[5]



Scheme 1. Nucleophile-mediated ring expansion of tetrahydropyrimidin-2-ones **2** into tetrahydro-1,3-diazepin-2-ones **1**.

In continuation of this research, we studied the thermal stability of solutions of 4-methoxy- (**3a-c**) and 4-phenylthio-substituted diazepinones (**3d-f**) and found that above 90–100 °C, these compounds eliminated MeOH or PhSH to give 2,3-dihydro-1*H*-1,3-diazepin-2-ones **4a-c** (Scheme 2).



Scheme 2. Thermolysis of 4-methoxy- and 4-phenylthio-substituted tetrahydro-1,3-diazepin-2-ones **3a-f**.

Initially, we studied the thermolysis of compounds **3a-f** using ^{1}H NMR spectroscopy. We heated DMSO-d_6 solutions of **3a-f** in NMR tubes at different temperatures and time intervals, and then determined the compositions of the reaction mixtures (at 25 °C). Selected data are summarized in Table 1.

Table 1 shows that thermolysis of tetrahydrodiazepinones **3a-f** resulted in the corresponding dihydrodiazepinones **4a-c** as the major products. Conversion of the starting material strongly depended

on the substituent at the C4 position. The rate of transformation of phenylthio diazepinones **3d-f** was lower than those of methoxy derivatives **3a-c** (entries 1, 2 and 6 vs entries 10, 11 and 13, respectively), probably due to the poorer leaving group ability of the phenylthio group compared with a methoxy group.

Table 1. Product distribution upon thermolysis of **3a-f** and **4a-c** in DMSO-d_6.

Entry	**3** *or* **4**	Temp,[a] (°C)	Time, (h)	Product distribution (%)[b] **3**	**4**	**5**	**6**	**7**	**8**
1	**3a**	132	0.5	0	91	7	0	2	-
2	**3b**	132	0.5	0	83	1	9	6	1
3	**3c**	98	2.2	13	59	1	24	3	-
4	**3c**	122	1.0	45	42	1	9	3	-
5	**3c**	122	2.0	0	42	1	35	22	-
6	**3c**	135	0.5	0	71	0	20	9	-
7	**3d**	98	2.2	43	46	9	1	1	-
8	**3d**	108	4.0	19	67	11	2	1	-
9	**3d**	108	7.3	0	71	16	7	6	-
10	**3d**	132	0.5	30	63	6	0	1	-
11	**3e**	132	0.5	55	40	3	1	1	0
12	**3e**	136	2.0	7	66	8	4	15	0
13	**3f**	132	0.5	69	27	2	2	0	-
14	**4a**	136	3.1	-	78	0	0	22	-
15	**4b**	136	4.7	-	32	0	9	59	0
16	**4c**	136	4.8	-	17	2	3	78	-

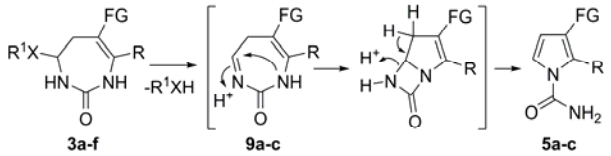
[a] Oil bath temperature (±1.5 °C).
[b] According to ^{1}H NMR spectroscopic data.

Some other products, 1-carbamoyl-1*H*-pyrroles **5a-c**, 1*H*-pyrroles **6a-c**, 3-(aminomethylene)-2,3-dihydro-1*H*-pyrrol-2-ones **7a-c**, and bis-diazepinone **8** (from **3b**) always formed along with products **4a-c**. The amounts of these products obtained depended on the structure of the starting material, the temperature and the reaction time. In general, increasing the temperature and decreasing the reaction time led to an increase in the relative amounts of **4a-c** (entries 3–6 and entries 8–10). Under the optimized conditions (entries 1, 2 and 6) the yields of **4a-c** from **3a-c** determined by ^{1}H NMR spectroscopy were 71–91%. These conditions were used for the preparative synthesis of diazepinones **4a-c**. Heating **3a-c** in DMSO at 135 °C for 30 minutes followed by the addition of water and filtration of the formed precipitate gave products **4a-c** in 53–73% yields after silica gel column chromatography.

Scheme 2 illustrates possible routes for the transformation of substrates **3** into compounds **4-8** upon heating. The additional ^{1}H NMR experiments showed that prolonged heating of dihydrodiazepinones **4a-c** in DMSO-d_6 at 136 °C led to their slow conversion, mainly into pyrrolones **7a-c** (entries 14–16). The summarized ^{1}H NMR spectroscopic data in Table 1 confirms that the thermolysis of **3a-f** proceeds via two independent pathways. Pathway **A** gives diazepinones **4a-c** followed by their slow transformation into pyrrolones **7a-c**; pathway **B** affords carbamoylpyrroles **5a-c**

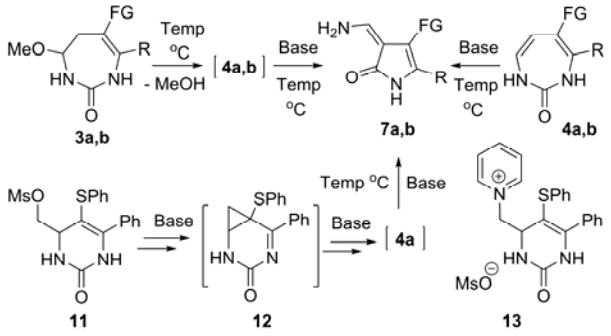
and then pyrroles **6a-c**. Formation of bis-diazepinone **8** upon heating of **3b** can be explained as a result of the reaction of **4b** with its imine tautomer **9b** (see refs 5a,b). We suppose that thermal elimination of MeOH from **3a-c** proceeds through formation of imine intermediates **9a-c** followed by a tautomeric shift of hydrogen to produce more stable enamines **4a-c**. Bis-diazepine **8** was not observed in the thermolysis of phenylthio-substituted diazepine **3e** (entries 11 and 12), presumably due to the short life-time of **9b** in the presence of strongly nucleophilic thiophenol. The rearrangement of dihydrodiazepinones **4a-c** into pyrrolones **7a-c** seems quite intriguing; its mechanism is currently under investigation and will be briefly described below.

There are several possible mechanisms underlying the transformation of tetrahydrodiazepinones **3a-f** into pyrroles **5a-c**. One of them could include hydrolysis of **3a-f** with traces of residual water in DMSO to produce hydroxy diazepines **3** (R^1X = OH) followed by ring-opening and recyclization. However, thermolysis of diazepines **3a,c,f** in refluxing toluene or xylene under strictly anhydrous conditions also gave significant amounts (up to 30%) of pyrroles **5a**,**c** in addition to diazepines **4a**,**c** and other products. Therefore, we think that compounds **5a-c** result from transannular attack of the N1 nitrogen at the carbon atom C4 of imine intermediates **9a-c** to produce derivatives of 1,6-diaza-bicyclo[3.2.0]hept-2-en-7-one followed by C5-N6 cleavage (Scheme 3).



Scheme 3. Plausible pathway for the transformation of tetrahydrodiazepinones **3a-f** into pyrroles **5a-c**.

Formation of pyrrolones **7a-c** from dihydrodiazepinones **4a-c** upon thermolysis is a new and quite unusual reaction of monocyclic 1,3-diazepines. To understand the mechanism of this reaction and develop preparative syntheses of pyrrolones **7**, we studied the reactivity of **4a,b** and their precursors, **3a,b** and **11**, using basic reagents with different solvents, temperatures and reaction times (Scheme 4).



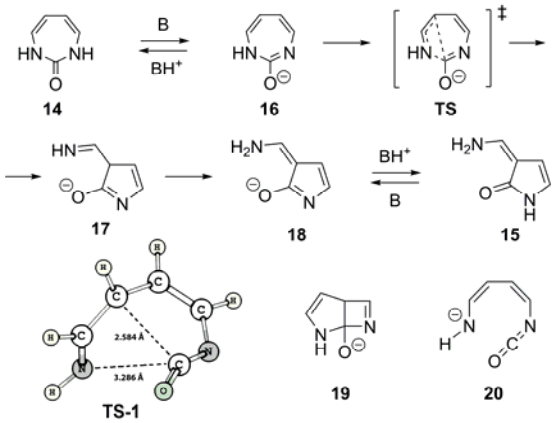
Scheme 4. Base-mediated transformations of **4a,b** and their precursors **3a,b** and **11** into pyrrolones **7a,b**.

Generally, the rate of the rearrangement of diazepinones **4a,b** into pyrrolones **7a,b** was increased significantly by bases and heating. Reflux of compounds **4a,b** in pyridine for 7–10 hours gave pyrrolones **7a,b** in excellent isolated yields (93–95%).

Since dihydrodiazepinones **4a,b** were obtained by thermal elimination of MeOH from tetrahydrodiazepinones **3a,b**, we attempted to synthesize pyrrolones **7a,b** directly from **3a,b**. Reflux of diazepine **3a** in pyridine for seven hours afforded pyrrolone **7a** in 77% yield after silica gel column chromatography. Under similar conditions diazepine **3b** gave pyrrolone **7b** in 92% yield.

Previously, we found that tetrahydropyrimidines **2**, in the presence of strong non-nucleophilic bases, were transformed into dihydrodiazepinones (e.g., **4** and **9**) via cyclopropane bicyclic intermediates (e.g., **12**).[5e] Reflux of **11** in pyridine for six hours in the presence of DBU (0.25 equiv) resulted in a mixture of pyrroles **5a**, **6a** and **7a**, and pyridinium salt **13** in a ratio of 1:13:78:8, respectively. Pyrrolone **7a** was isolated from this mixture using column chromatography in 37% yield. Compound **13** was the major product when pyrimidine **11** was refluxed in pyridine without DBU for two hours (**5a**:**6a**:**7a**:**13** = 4:5:39:52). Therefore, we assume that the basicity of pyridine is not sufficient for proton abstraction from $N_{(1)}H$, which promotes the ring expansion.[5e]

The base-mediated rearrangement of diazepinones **4a,b** into pyrrolones **7a,b** seems to be extraordinary. To our knowledge, there are no reports concerning this type of transformation. In order to understand its mechanism we performed quantum chemical calculations at the B3LYP/6-31+G(d,p) level of theory for the simplest model reaction, namely the rearrangement of diazepinone **14** into pyrrolone **15** (Scheme 5).



Scheme 5. A plausible pathway for the rearrangement of **14** into **15** and the calculated geometry of the transition state in pyridine solution (TS-1) (the C-C-C-C dihedral angle = -77.67°).

First, we studied the structure of **14** and its conjugated base **16**, from which the rearrangement presumably starts. The calculations showed that these compounds are the most stable among all the

possible tautomers (seven for **14** and three for **16**) in the gas phase and in DMSO or pyridine solutions using the polarizable continuum model (PCM). They are fully conjugated and their planar conformations could be expected to be anti-aromatic 8π-electron systems,[6] especially for **16**.

The nuclear-independent chemical shift[7] (NICS) values of **14** and **16** in the optimized and planar conformations were used as a magnetic criterion of aromaticity. The NICS(0) values in the gas phase calculated at the HF/6-31+G(d) level (2.55 and 1.29 ppm for the optimized conformations of **14** and **16**; 5.45 and 11.85 ppm for the planar conformations of **14** and **16**, respectively) show that molecules of **14** and **16** in the planar conformations are anti-aromatic. To avoid anti-aromaticity these compounds adopt boat-like conformations with the nitrogen of the NH group and carbons of the opposite double bond out of the plane. The B3LYP/6-31+G(d,p) calculations in the gas phase, DMSO or pyridine solutions including the intrinsic reaction coordinate[8] (IRC) analysis demonstrated that the planar conformations of **14** and **16** are transition states with only one imaginary vibrational frequency and energy barriers of 1.23–1.35 and 3.65–3.82 kcal/mol for **14** and **16**, respectively.

The anion **16** possesses an extraordinarily long (practically single) C2-NH bond (e.g., 1.490 Å in the gas phase) and a rather short C2-N bond (e.g., 1.331 Å in the gas phase) compared with the length of the C2-N bond (1.386 Å) in **14**. Therefore, cleavage of the C2-NH bond in **16** is most probably the first step of the rearrangement.

The B3LYP/6-31+G(d,p) calculations also using the PCM solvation model showed that the most favorable pathway for the rearrangement, after deprotonation of the NH group of **14**, is a concerted, one-step process including the C2-NH bond cleavage in **16** with simultaneous rotation around the C4-C5 single bond and proceeding via anionic transition states (TS) (Scheme 5). The IRC analysis demonstrated that the found transition states connect the desired minima. The energy barriers (from **16** to TS) were 30.27, 34.01 and 33.70 kcal/mol for the gas phase, DMSO and pyridine solutions, respectively (VZPE uncorrected). The product of this reaction, imino-derivative **17**, after the imine-enamine tautomerization into **18** followed by protonation was converted into the target compound **15**.

Rearrangement of dihydrodiazepinone anion **16** into pyrrolone anion **17** could also proceed via intermediate formation of 2,7-diazabicyclo[3.2.0]hepta-3,6-dien-1-olate (**19**) or conjugated base of (4-isocyanatobuta-1,3-dien-1-yl)amine (**20**) (Scheme 5). However, the B3LYP/6-31+G(d,p) calculations showed that the corresponding energy barriers lied significantly higher than that of the concerted process.

We assume that the above one-step mechanism is also valid for the base-promoted rearrangement of dihydrodiazepinones **4a,b** into pyrrolones **7a,b**. Indeed, the B3LYP/6-31+G(d,p) calculated structures of these compounds and their conjugated bases (the gas phase, DMSO and pyridine solutions) are close to those of **14** and **16**. In particular, the $N_{(3)}H$ deprotonated forms of **4a,b** adopt boat-like conformations with extraordinarily long C2-NH bonds (1.480–1.490 Å). The remarkable regioselectivity of the reaction proceeding exclusively via the $N_{(3)}H$ deprotonated forms of **4a,b** can be

explained by the higher acidity of the $N_{(3)}H$ group compared with that of the $N_{(1)}H$ group (0.54–2.32 kcal/mol). The calculations also showed that pyrrolones **7a,b** are much more stable (13.56–14.72 kcal/mol) than the corresponding dihydrodiazepinones **4a,b**.

Conclusion

New and convenient approach to functionalized 2,3-dihydro-1*H*-1,3-diazepin-2-ones based on thermal elimination of MeOH from 4-methoxy-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones has been developed. Upon heating with or without bases, dihydrodiazepinones underwent an unprecedented rearrangement into 3-(aminomethylene)-2,3-dihydro-1*H*-pyrrol-2-ones. A plausible mechanism for the rearrangement based on quantum chemical calculations involves initial NH deprotonation followed by a concerted ring-contraction process. 3-(Aminomethylene)-2,3-dihydro-1*H*-pyrrol-2-ones were also obtained from the precursors of 2,3-dihydro-1*H*-1,3-diazepin-2-ones as a result of cascade reactions.

Acknowledgements

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