Diastereoselectivity in the Ring Expansion of Tetrahydropyrimidin-2-ones into Tetrahydro-1*H*-1,3-diazepin-2-ones

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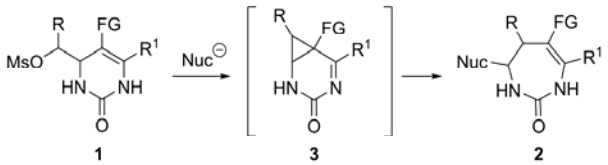
Abstract: A five-step synthesis of 4-(1-mesyloxyethyl)-6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one via amidoalkylation has been developed. Reaction of this compound with *C*-, *O*-, *S*-, and *N*-nucleophiles led to the highly diastereoselective formation of polysubstituted 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones as a result of ring expansion. The diastereoselectivity of the reaction depended on the nucleophile used and changed from *cis* to *trans*. The results obtained were explained by the formation of a bicyclic cyclopropane intermediate followed by cleavage of the zero bridge and stereoselective addition of the nucleophile to the resulting dihydro-1*H*-1,3-diazepin-2-one under kinetic control. The prepared *cis*-4-alkoxy-5-methyldiazepines reacted with alcohols under acidic conditions to give thermodynamically more stable *trans*-isomers.

Keywords: 1,2,3,4-Tetrahydropyrimidin-2-ones; 1*H*-1,3-Diazepin-2-ones; Amidoalkylation; Ring expansion

Introduction

The development of general approaches to rare heterocyclic scaffolds and studies on their structure and reactivity are important from the viewpoint of synthetic, theoretical, and medicinal chemistry. Monocyclic 1,3-diazepines and their partly hydrogenated derivatives are representatives of these scaffolds.[1] General strategies for their synthesis include various ring expansion reactions. Specifically, one-carbon ring expansion of 4-chloromethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates under the action of nucleophiles gave access to the correrssponding 2-oxo-2,3,6,7-tetrahydro-1*H*-1,3-diazepine-5-carboxylates.[2,3] However, this synthesis suffers from the poor availability of the starting materials.[3b,c] Based on our general approach to 1,2,3,4-tetrahydropyrimidin-2-ones/thiones[4] involving amidoalkylation of the enolates of α-functionalized ketones with *N*-(1-tosylalkyl)ureas and thioureas, we have developed a procedure for the synthesis of various 5-functionalized 4-(mesyloxymethyl)-1,2,3,4-tetrahydropyrimidin-2-ones **1** (Scheme 1, R = H), and have demonstrated that these compounds can serve as key precursors for the preparation of 1,3-diazepin-2-ones **2** (R = H).[5]

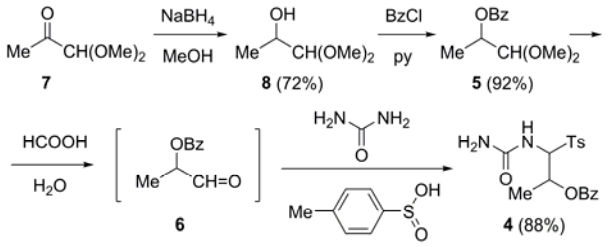


Scheme 1. Synthesis of 1,3-diazepin-2-ones **2** via ring expansion of tetrahydropyrimidin-2-ones **1** promoted by nucleophiles.

Our experimental data[5] and DFT calculations[5d] proved that the ring expansion of pyrimidines **1** into diazepines **2** proceeds through bicyclic cyclopropane intermediates **3**, which result from intramolecular nucleophilic substitution of the mesyloxy group by the anion formed after N(1)-H deprotonation. Intermediates **3** are very labile and undergo conversion into the final products **2** in the presence of nucleophiles via cleavage of the zero bridge. There are several pathways for the latter transformation.[5d] We hypothesized that investigation of the reaction diastereoselectivity might provide useful insights into the mechanism of the transformation. Thus, the synthesis of 4-(1-mesyloxyalk-1-yl)-1,2,3,4-tetrahydropyrimidin-2-ones **1** (R ≠ H) with two stereocenters and the study of nucleophile-mediated ring-expansion of these compounds into diazepines **2** (R ≠ H) is highly desirable. Herein, we describe the preparation of 4-(1-mesyloxyethyl)-6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one and its reactions with *C*-, *O*-, *S*-, and *N*-nucleophiles to give the corresponding 1,3-diazepin-2-ones. The mechanism of this reaction is discussed on the basis of the diastereoselectivity of the process. Some aspects of the structures and reactivity of the obtained diazepines are also reported.

Results and Discussion

According to our approach to tetrahydropyrimidin-2-ones,[4] we started this work with the preparation of the amidoalkylating reagent, sulfone **4** (Scheme 2).

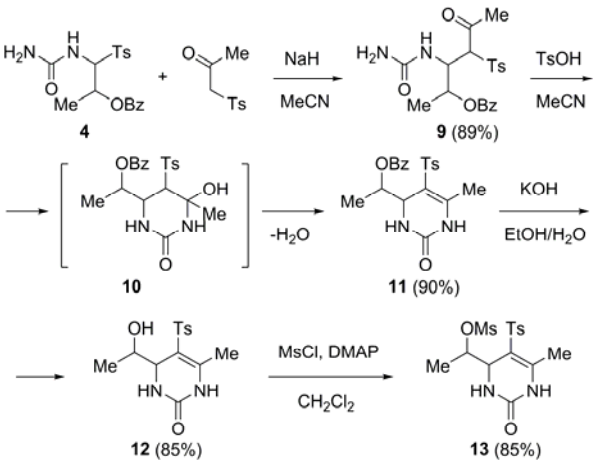


Scheme 2. Synthesis of the starting amidoalkylating reagent, sulfone **4**.

This compound was obtained from 2-benzoyloxypropanal dimethyl acetal (**5**), which was hydrolyzed (80% aqueous HCOOH, 40 °C, 4 h) to give the corresponding aldehyde **6**, followed by

addition of *p*-toluenesulfinic acid (1 equiv), urea (5 equiv) and water. The condensation was complete after 21 hours at room temperature to afford **4** in 88% yield as a mixture of two diastereomers in a ratio of 94:6. Sulfone **4** precipitated from the solution and was isolated in 95% purity by filtration (^{1}H NMR data). The crude product was used in the next step without further purification.

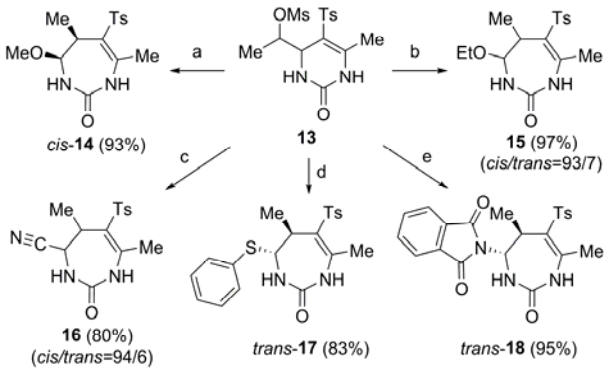
Sulfone **4** reacted with the sodium enolate of tosylacetone in dry MeCN at room temperature for 8 hours to give oxoalkylurea **9** in 89% yield as a mixture of four diastereomers in a ratio of 38:36:13:13 (Scheme 3). Heating **9** in MeCN at reflux for 2 hours in the presence of TsOH (0.5 equiv) resulted in cyclization to give hydroxypyrimidine **10**, dehydration of which afforded tetrahydropyrimidine **11** in 90% yield as a mixture of two diastereomers in a ratio of 52:48.



Scheme 3. Synthesis of the precursor for 1,3-diazepine synthesis, tetrahydropyrimidine **13**.

The benzoyl protection in **11** was removed under the action of KOH (5.3 equiv) in EtOH/H_2O (rt, 4 h) affording a 51:49 diastereomeric mixture of 4-(1-hydroxyethyl)pyrimidine **12** in 85% yield. The hydroxyl group in **12** was transformed into a mesyloxy group using MsCl (2 equiv) in the presence of DMAP (3 equiv) in CH_2Cl_2 (rt, 2 h). Pyrimidine **13** (two diastereomers in a ratio of 55:45) was isolated in 85% yield and 95% purity after extractive work-up (^{1}H NMR data), and this crude material was used in the subsequent ring-expansion step.

We studied the reactions of pyrimidine **13** with *O*-, *C*-, *S*-, and *N*-nucleophiles under conditions similar to those previously described.[5] Treatment of a 55:45 diastereomeric mixture of **13** with MeONa in MeOH (rt, 2.5 h) gave 4-methoxydiazepine **14** in 93% yield as a single *cis*-diastereomer (Scheme 4). 4-Ethoxydiazepine **15** was prepared analogously in 97% yield with excellent *cis*-diastereoselectivity (*cis*/*trans* = 93/7) from **13** and EtONa in EtOH (rt, 2 h).



Scheme 4. Nucleophile-promoted ring-expansion reactions of tetrahydropyrimidine **13**. Reagents and conditions: a) MeONa, MeOH, rt, 2.5 h; b) EtONa, EtOH, rt, 2 h; c) NaCN, DMSO, rt, 6 h; d) PhSH, NaH, THF, rt, 2 h; e) potassium phthalimide, MeCN, reflux, 1.5 h.

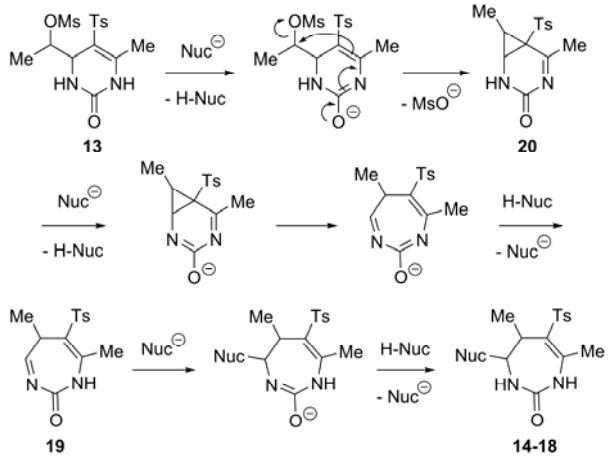
When pyrimidine **13** was reacted with NaCN (1.98 equiv) in dry DMSO at room temperature for 3.5 hours, the isolated material contained 10% of the minor diastereomer of the starting compound **13** along with the expected product of ring expansion, cyanodiazepine **16**. Reaction of compound **13** with NaCN (2.88 equiv) in DMSO at room temperature was complete in 6 hours to afford diazepine **16** in 80% yield as a 94:6 mixture of *cis*- and *trans*-diastereomers.

Pyrimidine **13** smoothly reacted with PhSNa (1.14 equiv) generated by treatment of PhSH with NaH in THF (rt, 2 h) to give the expected 4-(phenylthio)diazepine **17** in 83% yield after silica gel column chromatography. This compound was obtained as a single *trans*-isomer.

Full *trans*-diastereoselectivity was also observed in the reaction of pyrimidine **13** with potassium phthalimide (1.29 equiv) in refluxing MeCN over 1.5 hours to afford 4-(phthalimido)diazepine *trans*-**18** in 95% yield. The use of DMSO as the solvent did not change the selectivity of this reaction and gave *trans*-**18** in 82% yield (rt, 6 h).

The diazepine structures of the compounds **14-18** obtained were unambiguously established from their 1D and 2D NMR (^{1}H,^{1}H-COSY, ^{1}H,^{13}C-HSQC, ^{1}H,^{13}C-HMBC) spectra. In particular, the carbon chemical shifts of the C=C-CH_3 fragments in compounds **14-18** (115.5–117.4, 143.4–147.5, and 19.8–20.4 ppm in DMSO-d_6, respectively) are typical for tetrahydro-1,3-diazepin-2-ones, and not tetrahydropyrimidin-2-ones.

A plausible pathway for the nucleophile-mediated transformation of pyrimidine **13** into diazepines **14-18** based on our DFT calculations,[5d] reported experimental data,[5,6] and current results is shown in Scheme 5.



Scheme 5. A plausible pathway for the ring expansion of pyrimidine **13** to give diazepines **14-18**.

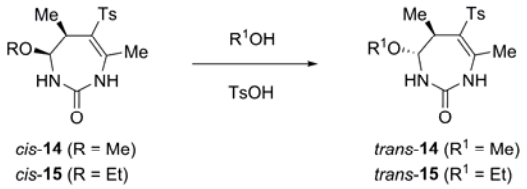
All the above ring-expansion reactions proceeded with full diastereoselectivity (for **14**, **17**, and **18**) or excellent diastereoselectivity (for **15**, **16**). Therefore, the formation of diazepines **14-18** from a 55:45 diastereomeric mixture of starting pyrimidine **13** proceeds through the same indermediate with one stereogenic center. Presumably, this intermediate could be dihydrodiazepine **19** arising from zero-bridge cleavage in bicyclic compound **20**. Thus, the diastereoselectivity of the ring-expansion reaction depends on the addition of nucleophiles to the C=N double bond of intermediate **19**.

To confirm the proposed mechanism, we attempted to detect presumed intermediates in the reaction of pyrimidine **13** (a 55:45 diastereomeric mixture) with NaCN (1.3 equiv) in DMSO-d_6 at 25 °C using ^{1}H NMR spectroscopy. The reaction was complete in 2.5 hours to give a 95:5 mixture of *cis*- and *trans*-**16**. After 70 minutes, 7% of starting material **13** (unreacted minor isomer) was observed. No intermediates were detected in the NMR experiment because of their short lifetimes under the experimental conditions employed.

Unexpectedly, the diastereoselectivity of the ring expansion was dependent on the nucleophile used and changed from a *cis*-process (for MeONa, EtONa, and NaCN) to a *trans*-process (for PhSNa and potassium phthalimide). This can be explained by the reactions of intermediate **19** with nucleophiles under kinetic control. Bulky aryl-containing nucleophiles attack at C-4 of **19** exclusively from the side opposite to the 5-Me group to give *trans*-diazepines **17** and **18**, while smaller nucleophiles attack from the same side of the 5-Me group to afford predominantly *cis*-diazepines **14-16**. Although the reasons behind the *cis*-selectivity are not clear, we consider that stereoelectronic effects might be one possibility.

Kinetic control of the reaction of compound **13** with MeONa and EtONa was confirmed by isomerization of the resulting *cis*-**14** and *cis*-**15** into the corresponding *trans*-isomers. Indeed, we have

found that stirring *cis*-**14** in MeOH (rt, 30 min) or *cis*-**15** in EtOH (reflux, 30 min) in the presence of TsOH (0.1 equiv) gave *trans*-**14** or *trans*-**15** in 87% and 97% yields, respectively (Scheme 6).



Scheme 6. Acid-catalyzed transformation of *cis*-**14** and *cis*-**15** into *trans*-**14** and *trans*-**15**.

We assume that this isomerization proceeds by an S_N1 mechanism through the formation of an acyliminium cation followed by addition of the nucleophile. Similarly, *cis*-**14** was converted into *trans*-**15** in 76% yield by heating in EtOH at reflux for 30 minutes.

The above data demonstrate that *cis*-**14** and *cis*-**15** resulting from the ring expansion of **13** are thermodynamically less stable than the corresponding *trans*-isomers. This was confirmed by the DFT calculations (B3LYP/6-31+G(d,p)) performed for various conformers of *cis*-**14** and *trans*-**14** in the gas phase and DMSO solution using the polarizable continuum model (PCM). The calculations showed that *trans*-**14** was more stable than *cis*-**14** (2.08 and 3.73 kcal/mol for the gas phase and DMSO solution, respectively). Analogously, we found that *trans*-**16** was more stable than *cis*-**16** (1.31 kcal/mol in the gas phase).

The stereochemistry of the diazepines **14-18** obtained was determined using ^{1}H NMR spectroscopy. Proton couplings in the N(3)H-C(4)H-C(5)H fragment of these compounds were the most diagnostic. For example, the values of the vicinal coupling constant between N(3)H and H-4 for *cis*-**14**,**15** (1.3-1.4 Hz) compared with those for *trans*-**14**,**15** (6.2 Hz) in DMSO-d_6 prove, that these compounds exist predominantly in puckered conformations with pseudo equatorial and pseudo axial orientation of the alkoxy groups, respectively. The position of the 5-Me group in *cis*-**14**,**15** and *trans*-**14**,**15** is pseudo axial, which follows from the absence of long-range coupling between H-5 and 7-CH_3 (see refs 5a-d). In addition, long-range couplings between N(3)H and H-5 (1.5 Hz) in *cis*-**14**,**15** were observed.

Conclusion

We have developed a five-step synthesis of 4-(1-mesyloxyethyl)-6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one and demonstrated that its reactions with *C*-, *O*-, *S*-, and *N*-nucleophiles give access to polysubstituted 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones. All the ring-expansion reactions proceeded with excellent diastereoselectivity, which depended on the nucleophile used and changed from a *cis*-process (for MeONa, EtONa, and NaCN) to a *trans*-process (for PhSNa and potassium

phthalimide). The results obtained are explained via formation of a bicyclic cyclopropane intermediate followed by zero-bridge cleavage and stereoselective addition of the nucleophile to the resulting dihydro-1*H*-1,3-diazepin-2-one under kinetic control. The prepared *cis*-4-alkoxy-5-methyldiazepines, in contrast to their 5-unsubstituted analogs, reacted with alcohols under acidic conditions to give the thermodynamically more stable *trans*-isomers.

Acknowledgments

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