A Novel Ring Expansion of Pyrimidines to 1,2,4-Triazepines

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Abstract

A base-promoted ring expansion of 3-amino-4-hydroxyhexahydropyrimidine-2-thiones into 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones has been developed. Experimental data and DFT calculations showed that the reaction proceeded through fast formation of intermediate acyclic isomers of pyrimidines followed by their slow cyclization into triazepines. The starting hydroxypyrimidines were prepared by reaction of α,β-unsaturated ketones or β-alkoxy ketones with HNCS followed by treatment of the obtained β-isothiocyanato ketones with hydrazine.

Keywords

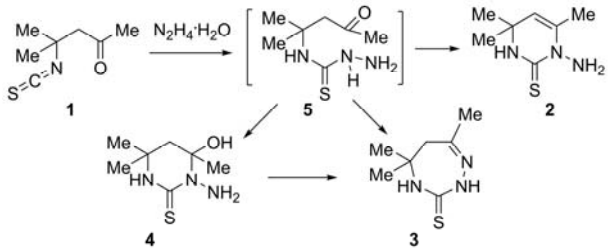
Isothiocyanato ketones; Thiosemicarbazides; Pyrimidines; Ring expansion; 1,2,4-Triazepines

Introduction

Rare heterocyclic scaffolds are of great interest from the viewpoint of synthetic, theoretical, and medicinal chemistry. With the exception of benzo- and hetero-fused derivatives, 1,2,4-triazepines, particularly 1,2,4-triazepin-2-ones/thiones are representative of these scaffolds.[1] Methods for the preparation of a few 1,2,4-triazepin-2-ones/thiones include reaction of arylidene ketones with $N_2H_4 \cdot 2HNCS$,[2] addition of (thio)semicarbazides to α,β-unsaturated ketones or their synthetic equivalents,[3] reaction of β-isocyanato or β-isothiocyanato ketones with hydrazines,[4,5] condensation of 1,3-dicarbonyl compounds with (thio)semicarbazides,[6] CDI-mediated cyclization of 3-hydrazino-substituted amines,[7] and reaction of thiosemicarbazides with dimethyl acetylenedicarboxylate and dibenzoyl acetylene.[8] The disadvantages of these methods are low availability of starting compounds, multistep reaction sequences, poor yields, limited synthetic flexibility, laborious procedures, etc. It should be noted that some 1,2,4-triazepin-2-ones are useful in the treatment of HIV infection.[7] However, low availability of non-fused 1,2,4-triazepin-2-ones/thiones hampers the progress of their investigation and application.

In continuation of our research into the synthesis of 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones using a ring expansion methodology,[9] we were interested in the preparation of their aza-analogs, 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones and their 3-thioxo derivatives. From the literature data[2,5]

we suggested that a straightforward and general approach to these heterocycles is based on the reaction of β-isothiocyanato ketones with hydrazines. This reaction was performed with 3-isothiocyanato-1,3-diphenylpropan-1-one,[5b,c] 2-(1-isothiocyanatocyclopentyl)cyclopentanone,[5a,d] and the readily available 4-isothiocyanato-4-methylpentan-2-one[5d,e] (**1**, Scheme 1) under neutral, acidic, or basic conditions.



Scheme 1. Reaction of isothiocyanate **1** with hydrazine.

It was demonstrated that isothiocyanate **1** reacts with hydrazine hydrate under heating in water in the presence of mineral acid to yield pyrimidine derivative **2** (Scheme 1).[10] Later it was reported that the product of this reaction is not the pyrimidine **2** but triazepine **3** which can also be prepared by reaction of isothiocyanate **1** with hydrazine hydrate in refluxing benzene using a Dean-Stark trap.[5e] In contrast, under the given conditions[5e,10] we obtained 3-aminopyrimidine-2-thione **4** as the major compound, and the amount of triazepinethione **3** did not exceed 5% and 15%, respectively (according to ^{1}H NMR spectra of the isolated crude products). This indicates that rapid cyclization of the intermediate thiosemicarbazide **5** into pyrimidine derivative **4** is followed by its slow transformation into triazepinethione **3** via ring expansion with nitrogen insertion. Therefore, results of the reaction of isothiocyanato ketones with hydrazines do not appear to be so clear as reported previously.[2,5,10] Indeed, the initially formed 4-(γ-oxoalkyl)thiosemicarbazides (e.g., **5**) can undergo various transformations, including cyclization into 1,2,4-triazepine-3-thiones, derivatives of pyrimidine, fused heterocyclic systems, macrocyclic compounds, etc.[11]

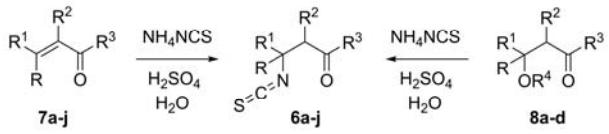
Based on the reported data and our experience, we hypothesized that 3-amino-4-hydroxyhexahydropyrimidine-2-thiones obtained by the reaction of β-isothiocyanato ketones with hydrazines can serve as starting compounds for the preparation of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones. Here, we report the synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones by base-promoted ring expansion of 3-amino-4-hydroxyhexahydropyrimidine-2-thiones, a plausible pathway of this transformation based on experimental data and DFT calculations, and oxidative

transformation of the obtained 1,2,4-triazepine-3-thiones into the corresponding 3-oxo derivatives. Two preparative procedures for the synthesis of β-isothiocyanato ketones are also reported.

Results and discussion

Preparation of β-isothiocyanato aldehydes and ketones was the first step of the triazepine synthesis. These isothiocyanates have been the focus of considerable attention since 1946,[12] and they have found a broad application as versatile precursors in organic synthesis.[13] The most general and straightforward preparative route to these compounds involves the addition of HNCS generated by treatment of thiocyanate salts with strong mineral acids to α,β-unsaturated aldehydes and ketones in water.[14–16] Success of this reaction is highly dependent on the substrate structure, particularly on the nature of the substituents.[14,15b] Therefore, in each particular case, careful optimization of reaction conditions should be carried out. As a consequence it is not surprising that the number of β-isothiocyanato aldehydes and ketones described still remains somewhat limited. For the present study, isothiocyanates **6a-j** were chosen as a starting material (Scheme 2, Table 1). Among them, only compounds **6a**,**j** could be considered to be synthetically available. As for other isothiocyanates, their synthesis was either not reported previously (for **6d**,**h,i**),[17] or they were obtained only as crude products (for **6e-g**),[5a,18,19] or procedures for their preparation were far from optimal (for **6b**,**c**).[15c,20]

Two alternative methods were used for the synthesis of starting isothiocyanates **6a-j**. The first method was based on the addition of HNCS to unsaturated carbonyl compounds **7a-j**, and the second was our original method involving the reaction of HNCS with β-alkoxy ketones **8a-d** (Scheme 2).



Scheme 2. Synthesis of β-isothiocyanato carbonyl compounds **6a-j**.

β-Alkoxy ketones **8a-d** were prepared by directed aldol type condensation of TMS ethers of acetone, cyclopentanone, or cyclohexanone with acetone dimethyl acetal or acetaldehyde diethyl acetal in the presence of $ZnCl_2$ in AcOEt.[21] During the reaction and vacuum distillation, β-alkoxy ketones **8a-c** partly converted into the corresponding unsaturated ketones **7b,d,h**. Compounds **6a-j** were synthesized by reacting **7a-j**, **8d** or mixtures of **7b,d,h** and **8a-c** with NH_4SCN in the presence of H_2SO_4 in water. The ratio of the reagents, the reaction temperature and time were optimized to achieve

maximum conversion of starting compounds (92–100% according to ^{1}H NMR spectra of the crude products) (Table 1).

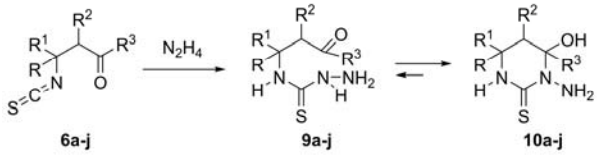
Table 1. Optimized reaction conditions for the synthesis of β-isothiocyanato carbonyl compounds **6a-j**[a]

Entry	**7** or/and **8** (**7**/**8** ratio)	Reagents ratio[b]	R	R^1	R^2	R^3	R^4	Temp (°C)[c]	Time (h)	**6**	Yield (%)[d]	Isomer ratio[e]
1	**7a**	1.05:0.53:1	Me	Me	H	Me	–	70–80	0.25	**6a**	75	–
2	**7b**+**8a** (3:97)	2.03:1.02:1	Me	H	H	Me	OEt	60	3	**6b**	81	–
3	**7c**	2.53:1.27:1	Me	H	Me	Me	–	60	4	**6c**	86	60:40
4	**7d**+**8b** (55:45)	2.11:1.06:1	Me	H	$CH_2CH_2CH_2$		OEt	60	4	**6d**	74	70:30
5	**7e**	3.01:1.51:1	Me	Me	$CH_2CH_2CH_2$		–	60	7	**6e**	74	–
6	**7f**	2.50:1.25:1	$CH_2CH_2CH_2$		$CH_2CH_2CH_2$		–	5	25	**6f**	62	–
7	**7g**	1.05:1.05:1	H	$CH_2CH_2CH_2CH_2$		Me	–	60	4	**6g**	59	56:44
8	**7h**+**8c** (13:87)	1.96:0.98:1	Me	H	$CH_2CH_2CH_2CH_2$		OEt	60	3	**6h**	90	63:37
9	**8d**	2.05:1.02:1	Me	Me	$CH_2CH_2CH_2CH_2$		OMe	60	3	**6i**	90	–
10	**7j**	1.41:0.71:1	Me	H	H	H	–	rt, then 40	1, then 1	**6j**	56	–

[a] Level of conversion of the starting material is 100% (entries 1, 2, 8–10), 96% (entry 3), 95% (entries 4, 5), and 92% (entry 6).
[b] NH_4SCN/H_2SO_4/substrate molar ratio.
[c] Bath temperature.
[d] Isolated yield (after vacuum distillation).
[e] After vacuum distillation.

Under improved reaction conditions mesityl oxide (**7a**) reacted with HNCS (1.05 equiv.) for 15 min upon heating at 70–80 °C to give isothiocyanate **6a** in 75% isolated yield (Table 1, entry 1). Isothiocyanato ketones **6b-e,h,i** were prepared using a greater excess of HNCS (1.96–3.01 equiv.) and heating at 60 °C for 3–7 hours (entries 2–5, 8, and 9). The same temperature was used for the preparation of isothiocyanate **6g** from ketone **7g** (entry 7). In contrast, the addition of HNCS to ketone **7f** smoothly proceeded at 5 °C for 25 h (entry 6). The amount of isothiocyanate **6f** in the isolated crude product significantly decreased within the reaction temperature range of 20–90 °C (^{1}H NMR spectroscopic data). Mild reaction conditions were applied for the synthesis of isothiocyanate **6j** from aldehyde **7j** (entry 10). Compounds **6c,d,g,h** with two stereocenters formed as diastereomeric mixtures (Table 1). The isothiocyanates **6a-j** obtained were purified by vacuum distillation. Partial elimination of HNCS proceeded during distillation of **6d,e,f,h** to give an admixture of the corresponding unsaturated ketone **7d,e,f,h** (3–21%) in the resulting product. The amount of this admixture was taken into account in the following synthetic step.

The reaction between isothiocyanates **6a-j** and hydrazine hydrate (1 equiv.) readily proceeded in MeCN or EtOH at room temperature to give the corresponding 3-amino-4-hydroxyhexahydro-pyrimidine-2-thiones **10a-j** in 74–97% yields (Scheme 3, Table 2) via intermediate formation of 4-(γ-oxoalkyl)thiosemicarbazides **9a-j**. Cyclization of the latter with participation of the amino group was not observed.



Scheme 3. Reaction β-isothiocyanato carbonyl compounds **6a-j** with hydrazine.

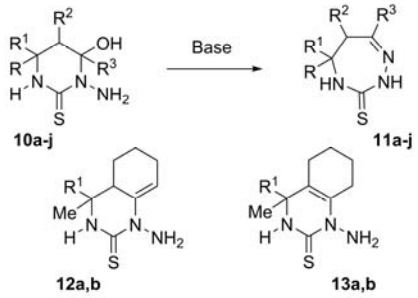
Table 2. Synthesis of 3-amino-4-hydroxyhexahydropyrimidine-2-thiones.[a]

Entry	**6**	Solvent	Time (h)[b]	Product(s)	Yield (%)[c]	Isomer ratio for **10**[d]
1	**6a**	EtOH	1	**10a**	93	–
2	**6b**	MeCN	1	**10b**+**9b**[e]	93	75:25
3	**6c**	MeCN	1	**10c**+**9c**[f]	91	45:26:18:11
4	**6c**	EtOH	1	**10c**+**9c**[f]	90	46:26:19:9
5	**6d**	MeCN	1.5	**10d**+**9d**[g]	82	71:26:2:1
6	**6e**	MeCN	2	**10e**	96	60:40
7	**6f**	MeCN	0.17	**10f**	93	60:40
8	**6g**	MeCN	1	**10g**+**9g**[h]	88	50:29:13:8
9	**6h**	MeCN	2.33	**10h**	96	36:35:27:2
10	**6i**	MeCN	2	**10i**	97	84:16
11	**6j**	EtOH	1	**10j**	74	90:10

[a] A slight excess of $N_2H_4 \cdot H_2O$ (up to 1.07 equiv.) was used, except for entry 6 (0.98 equiv.).
[b] At rt (entries 1–6, 8–11) or 0 °C (entry 7).
[c] Isolated yield (for **10** or **10**+**9**).
[d] According to ^{1}H NMR spectroscopic data for the crude product.
[e] **10b**/**9b** = 90:10.
[f] **10c**/**9c** (two isomers, 78:22) = 89:11.
[g] **10d**/**9d** (a single isomer) = 97:3.
[h] **10g**/**9g** (two isomers, 56:44) = 97:3.

Reaction of **6b-j** with hydrazine afforded pyrimidines as mixtures of two (for **10b,e,f,i,j**) or four diastereomers (for **10c,d,g,h**). This reaction proceeded under thermodynamic control, which was confirmed by data in entries 3 and 4, and by the presence of acyclic isomers **9b-d,g** along with pyrimidines **10b-d,g** (entries 2–5, 8) in the isolated products.

Pyrimidines **10a-j** were converted into the corresponding 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones **11a-j** under the action of bases (Scheme 4). Table 3 shows selected experimental data for this transformation.



Scheme 4. Base-promoted ring expansion of pyrimidines **10a-j** into triazepines **11a-j**.

Table 3. Base-promoted ring expansion of pyrimidines **10a-j** into triazepines **11a-j**.

Entry	**10**[a]	Solvent	Base (equiv.)	Reaction conditions (%)[b]	Conv.	Product(s) yield (%)	Isolated ratio[b]	Isomers
1	**10a**	H_2O	NaOH (0.74)	rt, 1.33 h	100	**11a**	93	–
2	**10b**	H_2O	NaOH (0.75)	rt, 3 h	100	**11b**	83	–
3	**10c**	H_2O	NaOH (1.00)	rt, 6 h	100	**11c**	78	55:45
4	**10d**	EtOH	KOH (2.51)	40 °C, 4 h	100	**11d**	90	92:8
5	**10e**	EtOH	KOH (2.49)	40 °C, 4 h	100	**11e**	91	–
6	**10f**	EtOH	KOH (2.50)	40 °C, 4 h	100	**11f**	93	–
7	**10f**	EtOH	KOH (2.52)	rt, 3 h	50	**11f**	–	–
8	**10g**	EtOH	KOH (2.50)	40 °C, 5.5 h	100	**11g**	93	93:7
9	**10g**	EtOH	KOH (2.02)	rt, 4 h	24	**11g**	–	92:8
10	**10g**	H_2O	NaOH (0.77)	rt, 1.5 h	0	–	–	–
11	**10g**	MeCN	DBU (0.54)	rt, 3 h	0	–	–	–
12	**10g**	EtOH–H_2O (10:1)	NaOH (1.02)	rt, 3.33 h, then reflux, 0.5 h	90	**11g**[c]	–	76:24
13	**10h**	MeOH	MeONa (2.56)	reflux, 5.5 h	100	**11h**	93	60:40
14	**10h**	EtOH	KOH (2.45)	40 °C, 5.5 h	52	**11h**	–	59:41
15	**10h**	EtOH	KOH (3.02)	60 °C, 5.5 h	100	**11h**[d]	–	62:38
16	**10h**	H_2O	KOH (3.04)	rt, 7 h 16 min	0	–	–	–
17	**10h**	EtOH	KOH (3.00)	40 °C, 24 h	70	**11h**[e]	–	60:40
18	**10h**	py	–	reflux, 3.42 h	100	**12a**+**13a**[f]	–	–
19	**10h**	py	DBU (0.25)	reflux, 3.42 h	0	–	–	–
20	**10h**	MeCN	DBU (0.24)	reflux, 2 h	0	–	–	–
21	**10i**	MeOH	MeONa (5.08)	reflux, 8 h	100	**11i**[g]	94	–
22	**10i**	MeOH	MeONa (5.01)	reflux, 7 h	96	**11i**[g]	–	–
23	**10i**	MeOH	MeONa (2.67)	reflux, 6.75 h	81	**11i**[h]	–	–
24	**10i**	EtOH	KOH (2.52)	40 °C, 5.5 h	5	**11i**	–	–
25	**10i**	THF	NaH (1.08)	rt, 6.42 h	3	**11i**	–	–
26	**10i**	py	–	reflux, 3.58 h	99	**12b**+**13b**[i]	–	–
27	**10i**	py	DBU (0.23)	reflux, 3.58 h	0	–	–	–
28	**10i**	MeCN	DBU (0.25)	reflux, 3 h	0	–	–	–
29	**10i**	toluene	DBU (0.25)	reflux, 3 h	0	–	–	–
30	**10j**	MeOH	MeONa (2.48)	40 °C, 5 h	80	—[j]	–	–
31	**10j**	EtOH	KOH (2.86)	40 °C, 4 h	90	—[j]	–	–

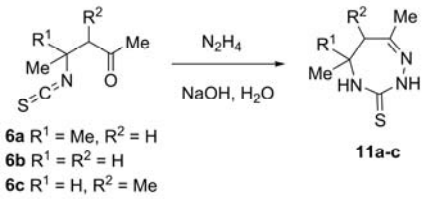
[a] The crude products obtained by the reaction of **6a-j** with N_2H_4 were used (see Table 2).
[b] Level of conversion according to ^{1}H NMR spectroscopy of the crude product.
[c] With considerable amount of impurities (about 55 mol%).
[d] With considerable amount of impurities (about 70 mol%).
[e] With considerable amount of impurities (about 66 mol%).
[f] A mixture of **12a** (R^1 = H, two isomers, 56:27) and **13a** (R^1 = H) in a ratio of 83:17.
[g] Plus 4 mol% of a mixture of **12b** and **13b** (R^1 = Me).
[h] Plus 5 mol% of a mixture of **12b** and **13b** (R^1 = Me).
[i] A mixture of **12b** and **13b** (R^1 = Me) in a ratio of 61:39.
[j] A complex mixture of unidentified products.

Monocyclic pyrimidines **10a-c** afforded triazepines **11a-c** in 78–93% yields after treatment with aqueous NaOH (0.74–1 equiv.) at room temperature (entries 1–3). Transformation of bicyclic pyrimidines **10d-g** into triazepines **11d-g** did not proceed under these conditions (entry 10). The use of alcoholic KOH (2.49–2.51 equiv.) and heating the reaction mixture at 40 °C for 4 h led to smooth formation of triazepines **11d-g** (entries 4–6, 8). For these starting compounds the reaction rate decreased with a decrease in temperature (entry 6 vs entry 7, and entry 8 vs entry 9), and reflux of the reaction mixture led to formation of a considerable amount of impurities (entry 12). No reaction proceeded with pyrimidine **10g** under the action of DBU in MeCN at room temperature (entry 11).

Treatment of perhydroquinazolines **10h,i** with KOH in EtOH upon heating (entries 14–16, 24), KOH in H_2O at room temperature (entry 17), NaH in THF at room temperature (entry 25), DBU in refluxing MeCN, pyridine, or toluene (entries 19–20, 27–29) did not result in formation of the target

bicyclic triazepines **11h,i**. Unexpected dehydration of compounds **10h,i** into the corresponding products **12a,b**, **13a,b** proceeded in refluxing pyridine (entries 18, 26) while in the presence of DBU this reaction was completely suppressed (entries 19, 27). Triazepines **11h,i** were prepared from perhydroquinazolines **10h,i** in refluxing MeOH in the presence of MeONa in 93–94% yields (entries 13, 21). It should be noted that complete conversion of **10h** required a greater amount of MeONa (5.08 equiv.) compared with **10i** (2.56 equiv.) (entry 13 vs entry 21; entry 21 vs entry 22 vs entry 23). Our attempts to obtain triazepine **11j** from **10j** under various conditions failed. Either the starting material was recovered or a complex mixture of unidentified products was formed (see, for example, entries 30 and 31).

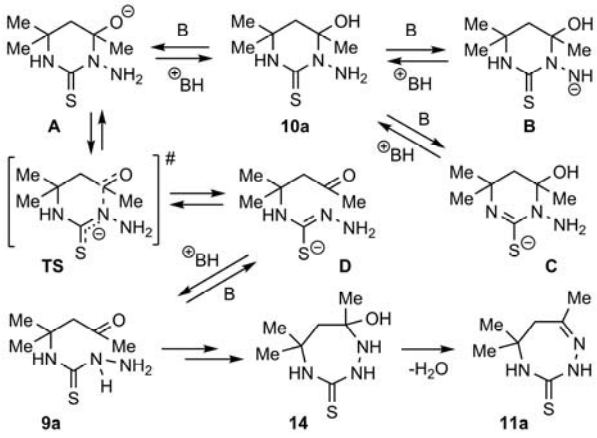
Monocyclic triazepines **11a-c** were also prepared using a one-pot procedure from β-isothiocyanato ketones **6a-c** without isolation of the intermediate pyrimidines **10a-c** (Scheme 5).



Scheme 5. One-pot synthesis of triazepinethiones **11a-c** from isothiocyanates **6a-c**.

Compounds **11a-c** were prepared in 75%, 61% and 42% isolated yield, respectively, by treatment of **6a-c** with hydrazine hydrate (1.02–1.11 equiv.) in the presence of NaOH (0.68–1.01 equiv.) in H_2O at room temperature for 1.5–6 h. Obviously, this transformation proceeds via fast reaction of N_2H_4 with isothiocyanato ketones **6a-c** to give pyrimidines **10a-c** followed by their slow conversion into the target products promoted with NaOH.

Thus, we have shown that 3-amino-4-hydroxyhexahydropyrimidine-2-thiones undergo previously unknown ring expansion to produce 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones in the presence of bases. Based on the experimental data shown in Table 3 and quantum chemical calculations at the B3LYP/6-311++G(d,p) level of theory using the PCM solvation model performed for the transformation of pyrimidine **10a** into triazepine **11a**, we suggest that this reaction includes initial deprotonation of compound **10a** under the action of a base to give one of three possible anions **A**, **B**, or **C** (Scheme 6).



Scheme 6. A plausible pathway for pyrimidine ring expansion.

The calculations showed that anion **B** is the most unstable compared with anions **A** and **C** (ΔG = 11.1–11.3 kcal/mol in EtOH, 298 K and 1 atm), therefore its formation can be excluded. Anions **A** and **C** are very close in energy (ΔG = 0.2 kcal/mol in EtOH), and they can form an equilibrium mixture upon deprotonation of **10a**. Since the only way for conjugated base **C** to be transformed into triazepine **11a** involves cleavage of C2–N3 bond with a high energy barrier, this anion seems to be the unreactive species. Anion **A** has an extraordinarily long N3–C4 bond and short C–O bond (1.625 and 1.316 Å in EtOH, respectively) compared with the lengths of the corresponding bonds in **10a** (1.484 and 1.426 Å in EtOH). Therefore, we suppose that deprotonation of **10a** to give anion **A** followed by cleavage of the N3–C4 bond is the most preferable initiation of the ring expansion.

Transformation of anion **A** into the anion of acyclic form **D** proceeds via the transition state **TS** with low activation energy (electronic energy 0.5 kcal/mol in EtOH, the Gibbs free energy ≈0 kcal/mol in EtOH, 298 K and 1 atm). Further detailed calculations using the OH-anion as a base showed that the complex of anion **A** with H_2O obtained after deprotonation of **10a** with hydroxide undergoes N3–C4 bond cleavage with an activation barrier of ΔG = 2.4 kcal/mol (EtOH, 298 K, 1 atm) to give the complex of anion **D** with H_2O. This reaction proceeds with a ΔG value of –1.1 kcal/mol. The IRC analysis demonstrated that the found transition state connects the desired minima. Anion **D** after protonation followed by cyclization of the obtained thiosemicarbazide **9a** into triazepine **14** and dehydration gives the target product **11a**. Formation of triazepine **11a** from pyrimidine **10a** is a thermodynamically favorable process with ΔG = –12 kcal/mol (EtOH, 298 K, 1 atm).

We suppose that the base-promoted transformation of other pyrimidines **10b-i** into the corresponding triazepines **11b-i** proceeds via acyclic isomers **9b-i** analogously, as described for **10a**. Although the acyclic isomers **9a-i** readily form from pyrimidines **10a-i**, their conversion into **14a-i**

proceeding with participation of the most nucleophilic nitrogen of the thiosemicarbazide moiety[22] seems to be slow and strongly dependent on the structure of the starting compound (Table 3). This explains the formation of side products from **10j** rather then triazepine **11j**, since the aldehyde group in the intermediate acyclic form **9j** is highly reactive under strongly basic conditions.

Conclusion

An efficient synthesis of the rare heterocyclic scaffold, 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thione has been developed. The key step of the synthesis is the ring expansion of 3-amino-4-hydroxy-hexahydropyrimidine-2-thiones under the action of bases. The proposed reaction pathway based on experimental data and DFT calculations included fast formation of intermediate acyclic isomers followed by their slow cyclization into triazepines. Starting hydroxypyrimidines were prepared by reaction of α,β-unsaturated ketones or β-alkoxy ketones with thiocyanic acid followed by treatment of the obtained β-isothiocyanato ketones with hydrazine. 3-Oxo-analogs were readily obtained from triazepine-3-thiones by oxidation with H_2O_2. Since various β-alkoxy ketones can be prepared using directed aldol condensation of TMS ethers of ketones and acetals of carbonyl compounds, a large variety of triazepines can be obtained and subsequently modified. We believe that this methodology will be helpful for further research into the chemistry and applications of 1,2,4-triazepines.

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