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Base-promoted ring expansion of 3-aminopyrimidine-2-thiones into 1,2,4-triazepine-3-thiones

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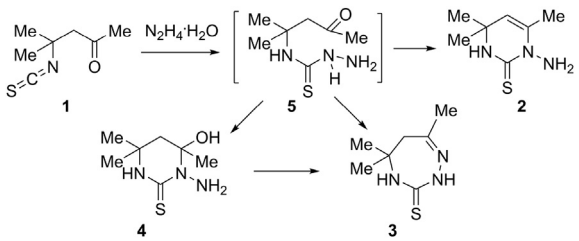
ABSTRACT

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. Triazepine-3-thiones were transformed into their 3-oxo analogs by oxidation with H_2O_2 under basic conditions.

1. 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,[5c,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-

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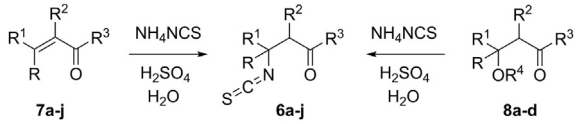
aminopyrimidine-2-thione **4** as the major compound, and the amount of triazepinethione **3** did not exceed 5% and 15%, respectively (according to ^{1}H NMR spectra of the isolated crude products). This indicates that rapid cyclization of the intermediate thiosemicarbazide **5** into pyrimidine derivative **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.

2. Results and discussion

2.1. Synthesis of starting β-isothiocyanato carbonyl compounds

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**),[17,25] 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**).[15b,20]



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

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).

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).

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 h (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.

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.

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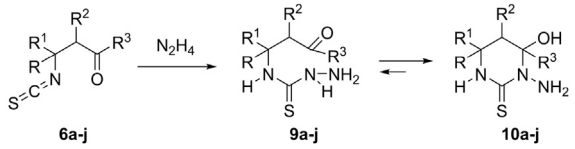
2.2. Synthesis of 3-amino-4-hydroxyhexahydropyrimidine-2-thiones

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-hydroxyhexahydropyrimidine-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.

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.



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

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

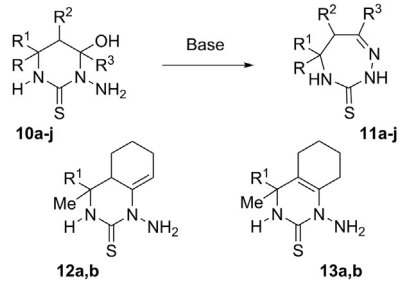
Entry	6	Solvent	Time (h)[b]	Product(s)	Yield (%)[c]	Isomer ratio for 10[d]
1	**6a**	EtOH	1	**10a**	93	—
2	**6b**	MeCN	1	**10b**+**9b**[e]	93	75:25
3	**6c**	MeCN	1	**10c**+**9c**[f]	91	45:26:18:11
4	**6c**	EtOH	1	**10c**+**9c**[f]	90	46:26:19:9
5	**6d**	MeCN	1.5	**10d**+**9d**[g]	82	71:26:2:1
6	**6e**	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.

2.3. Synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones/ones

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.

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),



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

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).

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).

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

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

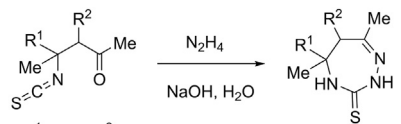
Entry	10[a]	Solvent	Base (equiv)	Reaction conditions	Conv. (%)[b]	Product(s)	Isolated yield (%)	Isomers ratio[b]
1	**10a**	H_2O	NaOH (0.74)	rt, 1.33 h	100	**11a**	93	—
2	**10b**	H_2O	NaOH (0.75)	rt, 3 h	100	**11b**	83	—
3	**10c**	H_2O	NaOH (1.00)	rt, 6 h	100	**11c**	78	55:45
4	**10d**	EtOH	KOH (2.51)	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.

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** rapidly form from pyrimidines **10a**–**i**, their cyclization into **14a**–**i**, which proceeds 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



6a R^1 = Me, R^2 = H
6b R^1 = R^2 = H
6c R^1 = H, R^2 = Me

11a-c

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

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.

3-Oxo-analogs of the obtained 1,2,4-triazepine-3-thiones can be readily prepared by oxidation.

Compounds **11a**,**f**,**g**,**i** were oxidized with H_2O_2 in H_2O–EtOH solution in the presence of KOH to give the corresponding 1,2,4-triazepin-3-ones **15a**–**d** in high yields (Scheme 7).

3. 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-

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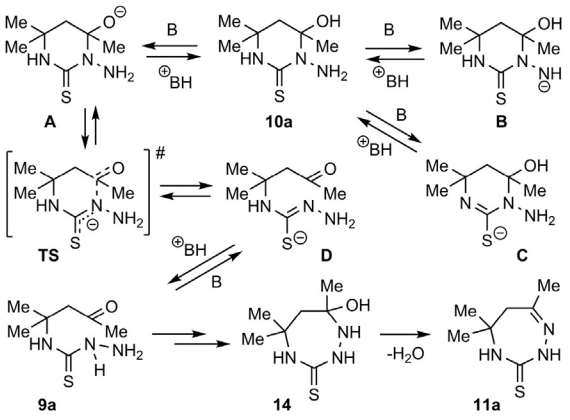
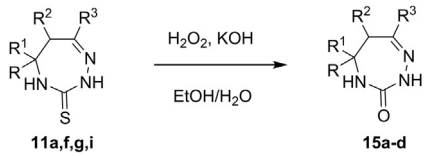


Scheme 6. A plausible pathway for pyrimidine ring expansion.



11a, **15a** R = R^1 = R^3 = Me, R^2 = H.
11f, **15b** R + R^1 = R^2 + R^3 = $(CH_2)_3$.
11g, **15c** R = H, R^1 + R^2 = $(CH_2)_4$, R^3 = Me.
11i, **15d** R = R^1 = Me, R^2 + R^3 = $(CH_2)_4$.

Scheme 7. Oxidation of triazepinethiones **11a**,**f**,**g**,**i** into triazepinones **15a**–**d**.

hydroxyhexahydropyrimidine-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.

4. Experimental section

4.1. General

All solvents were distilled before use. 95% EtOH was used unless otherwise indicated. The petroleum ether had a distillation range of 40–60 °C. 100% hydrazine hydrate was used. Mixtures of **8a** and **7b** (97:3), **8b** and **7d** (45:55), and **8c** and **7h** (87:13) were prepared according to the literature procedure[21] by the reaction of acetaldehyde diethyl acetal with the TMS ethers of acetone, cyclopentanone, and cyclohexanone, respectively, in the presence of $ZnCl_2$ in AcOEt followed by vacuum distillation of the resulting products (see Supplementary data). Compounds **7e** and **8d** were obtained analogously by condensation of acetone dimethyl acetal with the TMS ethers of cyclopentanone and cyclohexanone (see Supplementary data). All other reagents were purchased from commercial sources and used without additional purification. IR spectra (Nujol) were recorded using a BrukerVector 22 spectrophotometer. Band characteristics in the IR spectra are defined as very strong (vs), strong (s), medium (m), weak (w), and shoulder (sh). ^{1}H NMR and proton decoupled ^{13}C NMR spectra (solutions in DMSO-d_6 or $CDCl_3$) were acquired using a Bruker DPX 300 spectrometer at 300.13 MHz (^{1}H) and 75.48 MHz (^{13}C). ^{1}H NMR chemical shifts are referenced to the residual proton signal in DMSO-d_6 (2.50 ppm) or $CDCl_3$ (7.24 ppm). In ^{13}C NMR spectra, central signals of DMSO-d_6 (39.50 ppm) or $CDCl_3$ (77.23 ppm) were used as references. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), and some combinations of these, multiplet (m). Selective ^{1}H–^{1}H decoupling and DEPT-135 experiments were used to aid in the assignment of ^{1}H and ^{13}C NMR signals. 2D NMR experiments (^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC) for compounds **11a**–**c** (solutions in DMSO-d_6) were carried out using a Bruker Avance-600 spectrometer at 600.13 MHz (^{1}H) and 150.91 MHz (^{13}C). Mass spectra were obtained on a Finnigan MAT INCOS 50 instrument (electron impact, 70 eV). Elemental analyses (CHN) were performed using a Thermo Finnigan Flash EA1112 apparatus. Thin-layer chromatography was carried out on Aldrich silica gel 60 F254 aluminum backed plates in $CHCl_3$/MeOH (9:1, v/v) and $CHCl_3$/MeOH (5:1, v/v) as solvent systems. Spots were visualized with UV light or iodine vapors. Column chromatography was performed with Macherey–Nagel silica gel 60 (0.063–0.200 mm). All yields refer to isolated, spectroscopically and TLC pure compounds. The color of solid substances was white, if not otherwise mentioned. pH of aqueous solutions was measured with universal indicator paper.

4.2. Synthesis of β-isothiocyanato carbonyl compounds

*4.2.1. 4-Isothiocyanato-4-methylpentan-2-one (**6a**).* To a stirred mixture of 4-methylpent-3-en-2-one (**7a**) (131.24 g, 1.337 mol) and NH_4SCN (106.91 g, 1.404 mol) in H_2O (130 mL) was added a cooled (10–15 °C) solution of H_2SO_4 (40.0 mL, 0.702 mol; d=1.831 g/mL, 94%) in H_2O (40 mL) over 5 min. The obtained emulsion was heated in a water bath (70–80 °C, temperature of bath) under intense stirring for 15 min, and cooled. The organic layer was separated, and the aqueous layer was extracted with ether (2×45 mL). The combined organic layer was neutralized with 7% aqueous Na_2CO_3 to pH 8, washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was distilled under vacuum to give compound **6a** (158.71 g, 75%) as a slightly yellow liquid. Bp 102–113 °C/20 mmHg; n_D^{20} 1.5008 (lit.[23] 1.5030). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 2.69 (2H, s, CH_2), 2.15 (3H, s, CH_3C=O), 1.46 (6H, s, $2CH_3$).

*4.2.2. 4-Isothiocyanatopentan-2-one (**6b**).* To a stirred solution of a 97:3 mixture of 4-ethoxypentan-2-one (**8a**) and pent-3-en-2-one (**7b**) (19.92 g, 154.65 mmol total) and NH_4SCN (23.90 g, 313.97 mmol) in H_2O (70 mL) was added a cooled (10–15 °C) solution of H_2SO_4 (9 mL, 158.07 mmol; d=1.831 g/mL, 94%) in H_2O (35 mL) over 5 min. The obtained emulsion was heated in a water bath (60 °C, temperature of bath) under intense stirring for 3 h, and cooled. The resulting mixture was extracted with ether (100 mL, 2×50 mL) using 0.5 L separatory funnel. To the combined organic layer was gradually added saturated aqueous $NaHCO_3$ (50 mL) and then solid $NaHCO_3$ was added in small portions so that the foam formation was not too intense. After the neutralization was almost completed, which could be detected by the fading of gas evolution, the aqueous layer was separated, and the organic layer was additionally washed with saturated aqueous $NaHCO_3$ (2×50 mL, 25 mL) to pH 8, H_2O (2×50 mL), brine (2×50 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was distilled under vacuum with argon bleed to give compound **6b** (18.03 g, 81%) as a slightly yellow liquid in thick layer. Bp 58–67 °C/0.1 mmHg, n_D^{20} 1.5079 (lit.[20] 1.5074). After about 4 weeks of storage at 5–7 °C the color of liquid becomes more intense, which has no

effect on the yields or color of products prepared from it. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 4.21 (1H, ddq, ^3J=7.2, ^3J=6.6, ^3J=5.9 Hz, CHN), 2.83 (1H, dd, ^2J=17.5, ^3J=7.2 Hz, H_A in CH_2), 2.60 (1H, dd, ^2J=17.5, ^3J=5.9 Hz, H_B in CH_2), 2.15 (3H, s, CH_3C=O), 1.34 (3H, d, ^3J=6.6 Hz, CH_3).

*4.2.3. 4-Isothiocyanato-3-methylpentan-2-one (**6c**).* To a stirred mixture of 3-methylpent-3-en-2-one (**7c**) (24.88 g, 253.52 mmol) and NH_4SCN (48.86 g, 641.88 mmol) in H_2O (100 mL) was added a cooled (10–15 °C) solution of H_2SO_4 (18.3 mL, 321.13 mmol; d=1.831 g/mL, 94%) in H_2O (50 mL) in small portions (0.5–1 mL) over 7 min. The obtained emulsion was heated in a water bath (60 °C, temperature of bath) under intense stirring for 4 h, and cooled. The resulting mixture was extracted with ether (100 mL, 3×50 mL). Neutralization of combined organic layer was performed as described for compound **6b**. After neutralization the organic layer was washed with H_2O (2×50 mL), brine (2×50 mL, 25 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue containing **6c** (two isomers, 63:37) and **7c** in a ratio of 96:4 was distilled under vacuum with argon bleed to give compound **6c** (34.27 g, 86%; a slightly yellow liquid in a thick layer) as a 60:40 mixture of two isomers. Bp 65–75 °C/0.1 mmHg; n_D^{20}=1.5072 (lit.[20] 1.5078). ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 4.06 (1H, dq, ^3J=7.1, ^3J=6.5 Hz, CHN), 2.60 (1H, dq, ^3J=7.1, ^3J=7.1 Hz, CHC=O), 2.15 (3H, s, CH_3C=O), 1.30 (3H, d, ^3J=6.5 Hz, CH_3CHN), 1.21 (3H, d, ^3J=7.1 Hz, CH_3CHC=O); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 4.00 (1H, dq, ^3J=7.2, ^3J=6.6 Hz, CHN), 2.73 (1H, dq, ^3J=7.2, ^3J=7.2 Hz, CHC=O), 2.17 (3H, s, CH_3C=O), 1.30 (3H, d, ^3J=6.6 Hz, CH_3CHN), 1.10 (3H, d, ^3J=7.2 Hz, CH_3CHC=O); ^{13}C NMR of the major isomer (75.48 MHz, $CDCl_3$) δ: 208.58 (C=O), 132.01 (NCS), 54.86 (CHN), 52.54 (*C*HC=O), 29.38 (*C*H_3C=O), 20.51 (*C*H_3CHN), 13.39 (*C*H_3CHC=O); ^{13}C NMR of the minor isomer (75.48 MHz, $CDCl_3$) δ: 208.78 (C=O), 132.28 (NCS), 54.59 (CHN), 52.30 (*C*HC=O), 29.36 (*C*H_3C=O), 18.71 (*C*H_3CHN), 12.84 (*C*H_3CHC=O).

*4.2.4. 2-(1-Isothiocyanatoethyl)cyclopentanone (**6d**).* To a stirred 45:55 mixture of 2-(1-ethoxyethyl)cyclopentanone (**8b**) and 2-ethylidenecyclopentanone (**7d**) (38.74 g, 295.98 mmol in total) and NH_4SCN (47.48 g, 623.75 mmol) in H_2O (120 mL) was added a cooled (10–15 °C) solution of H_2SO_4 (17.8 mL, 312.36 mmol; d=1.831 g/mL, 94%) in H_2O (50 mL) over 5 min. The obtained emulsion was heated in a water bath (60 °C, temperature of bath) under intense stirring for 4 h, and cooled. The resulting mixture was extracted with ether (150 mL, 2×50 mL). Neutralization of the combined organic layer was performed as described for compound **6b**. After neutralization the organic layer was washed with H_2O (3×50 mL), brine (2×30 mL, 15 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue containing **6d** (two isomers, 68:32) and **7d** in a ratio of 95:5 was distilled under vacuum from the flask equipped with a short-path distillation head and argon bleed tube to give a 88:12 mixture (40.34 g) of compound **6d** (two isomers, 70:30) and **7d** as a yellow liquid. Partial elimination of HNCS proceeded during distillation. The calculated yield of **6d** is 74% (37.05 g). Bp 72–97 °C/0.1 mmHg; n_D^{20}=1.5277. ^{1}H NMR of the 70:30 isomer mixture (300.13 MHz, DMSO-d_6) δ: 4.26 (0.7H, dq, ^3J=6.8, ^3J=3.4 Hz, CHN in the major isomer), 4.08 (0.3H, dq, ^3J=6.7, ^3J=4.3 Hz, CHN in the minor isomer), 1.37 (2.1H, d, ^3J=6.8 Hz, CH_3 in the major isomer), 1.29 (0.9H, d, ^3J=6.7 Hz, CH_3 in the minor isomer), 1.98–2.57, 1.66–1.93 (5H and 2H respectively, two m, $CH_2CH_2CH_2$ and CHC=O in the both isomers).

*4.2.5. 2-(2-Isothiocyanatoprop-2-yl)cyclopentanone (**6e**).* To a stirred mixture of 2-isopropylidenecyclopentanone (**7e**) (11.89 g, 95.71 mmol) and NH_4SCN (21.91 g, 287.83 mmol) in H_2O (45 mL) was added a cooled (10–15 °C) solution of H_2SO_4 (8.25 mL, 144.77 mmol; d=1.831 g/mL, 94%) in H_2O (25 mL) over 4 min. The obtained emulsion was heated in a water bath (60 °C, temperature of bath) under intense stirring for 7 h, and cooled. The resulting mixture was extracted with ether (50 mL, 3×30 mL). Neutralization of combined organic layer was performed as described for compound **6b**. After neutralization, the organic layer was washed with H_2O (3×30 mL), brine (2×30 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue containing **6e** and **7e** in a ratio of 95:5 was distilled twice under vacuum from the flask equipped with a short-path distillation head and argon bleed tube (first distillation gave a brown colored material; second distillation afforded a slightly yellow liquid in a thick layer) to give a 92:8 mixture (13.71 g) of compound **6e** and **7e**. Partial elimination of HNCS proceeded during distillation. The calculated yield of **6e** is 74% (12.95 g). Bp (first distillation) 81–102 °C/0.1 mmHg, bp (second distillation) 89–91 °C/0.1 mmHg; n_D^{20}=1.5239. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 1.57–2.33 (7H, m, $CH_2CH_2CH_2$ and CHC=O), 1.45 (3H, s CH_3), 1.42 (3H, s CH_3); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ: 215.98 (C=O), 131.97 br (NCS), 61.77 (C–N), 57.19 (*C*HC=O), 39.76 (CH_2), 28.96 (CH_3), 26.70 (CH_2), 26.37 (CH_3), 19.77 (CH_2).

*4.2.6. 2-(1-Isothiocyanatocyclopentyl)cyclopentanone (**6f**).* To a cooled (ice bath), stirred mixture of 2-cyclopentylidenecyclopentanone (**7f**) (15.18 g, 101.05 mmol) and NH_4SCN (19.24 g, 252.75 mmol) in H_2O (40 mL) was added a cooled (10–15 °C) solution of H_2SO_4 (7.4 mL, 126.68 mmol; d=1.825 g/mL, 92%) in H_2O (20 mL) over 7 min. The obtained emulsion was stirred in an ice bath for 2 h, and then allowed to stand at 5–7 °C (refrigerator) for 23 h. The resulting mixture was extracted with ether (60 mL, 2×20 mL). Neutralization of the combined organic layer was performed as described for compound **6b**. After neutralization the organic layer was washed with H_2O (3×25 mL), brine (2×25 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue containing **6f** and **7f** in a ratio of 92:8 was distilled under vacuum from the flask equipped with a short-path distillation head and argon bleed tube to give a 79:21 mixture (15.68 g) of compound **6f** and **7f** as a slightly yellow liquid in a thick layer. Partial elimination of HNCS proceeded during distillation. The calculated yield of **6f** is 62% (13.17 g). Bp 106–118 °C/0.1 mmHg; n_D^{20}=1.5433. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 1.59–2.42 (15H, m, all protons); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ: 216.43 (C=O), 132.62 br (NCS), 72.84 (C–N), 55.92 (CH_2), 39.88 (CH_2), 39.32 (CH_2), 38.42 (CH_2), 27.12 (CH_2), 23.40 (CH_2), 22.23 (CH_2), 20.30 (CH_2).

*4.2.7. 1-Acetyl-2-isothiocyanatocyclohexane (**6g**).* To a stirred mixture of 1-acetylcyclohexene (**7g**) (16.75 g, 134.88 mmol) and NH_4SCN (10.78 g, 141.61 mmol) in H_2O (11 mL) was added a cooled (10–15 °C) solution of H_2SO_4 (8.3 mL, 142.09 mmol; d=1.825 g/mL, 92%) in H_2O (15 mL) over 30 min. The obtained emulsion was heated in a water bath (60 °C, temperature of bath) under intense stirring for 4 h, and cooled. The resulting mixture was extracted with ether (20 mL, 2×10 mL). Neutralization of the combined organic layer was performed as described for compound **6b**. After neutralization the organic layer was washed with H_2O (3×20 mL), brine (2×20 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was distilled under vacuum from the flask equipped with a short-path distillation head and argon bleed tube to give compound **6g** (14.47 g, 59%; a yellow liquid) as a mixture of two diastereomers in a ratio of 56:44. Bp 90–114 °C/0.1 mmHg. ^{1}H NMR of the 56:44 isomer mixture (300.13 MHz, $CDCl_3$) δ: 4.36 (0.56H, unresolved m, half-width at half-height value of 8.0 Hz, CHN in the major isomer), 3.79 (0.44H, ddd, ^3J=10.9, ^3J=10.0, ^3J=4.2 Hz, CHN in the minor isomer), 2.62 (0.44H, ddd, ^3J=11.2, ^3J=10.0, ^3J=3.8 Hz, CHC=O in the minor isomer), 2.36 (0.56H, ddd, ^3J=12.1, ^3J=3.6, ^3J=3.0 Hz, CHC=O in the major isomer), 2.20 (1.32H, s, CH_3 in the minor isomer), 2.16 (1.68H, s, CH_3 in

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the major isomer), 1.15–2.23 (8H, m, $CH_2CH_2CH_2CH_2$ in the both isomers); ^{13}C NMR of the major isomer (75.48 MHz, $CDCl_3$) δ: 207.52 (C=O), 56.43 (CHN), 53.78 (*C*HC=O), 32.24 (CH_2), 28.04 (CH_3), 24.68 (CH_2), 22.95 (CH_2), 20.38 (CH_2), signal of the C=S carbon was not detected in the spectrum; ^{13}C NMR of the minor isomer (75.48 MHz, $CDCl_3$) δ: 208.91 (C=O), 56.17 (CHN), 54.82 (*C*HC=O), 32.88 (CH_2), 29.69 (CH_3), 27.99 (CH_2), 24.47 (CH_2), 24.03 (CH_2), signal of the C=S carbon was not detected in the spectrum.

*4.2.8. 2-(1-Isothiocyanatoethyl)cyclohexanone (**6h**).* To a stirred 87:13 mixture of 2-(1-ethoxyethyl)cyclohexanone (**8c**) and 2-ethylidenecyclohexanone (**7h**) (35.69 g, 217.27 mmol total) and NH_4SCN (32.35 g, 424.98 mmol) in H_2O (100 mL) was added a cooled (10–15 °C) solution of H_2SO_4 (12.15 mL, 213.21 mmol; d=1.831 g/mL, 94%) in H_2O (50 mL) over 10 min. The obtained emulsion was heated in a water bath (60 °C, temperature of bath) under intense stirring for 3 h, and cooled. The resulting mixture was extracted with ether (150 mL, 2×50 mL). Neutralization of the combined organic layer was performed as described for compound **6b** in a 1 L separatory funnel. After neutralization the organic layer was washed with H_2O (3×50 mL), brine (2×50 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue containing **6h** (two isomers, 62:38) was distilled under vacuum from the flask equipped with a short-path distillation head and argon bleed tube to give a 97:3 mixture (36.58 g) of compound **6h** (two isomers, 63:37) and **7h** as a yellow liquid. Partial elimination of HNCS proceeded during distillation. The calculated yield of **6h** is 90% (35.83 g). Bp 95–115 °C/0.1 mmHg; n_D^{20}=1.5359. ^1H NMR of the 63:37 isomer mixture (300.13 MHz, $CDCl_3$) δ: 4.25 (0.63H, dq, ^3J=6.6, ^3J=5.7 Hz, CHN in the major isomer), 4.21 (0.37H, dq, ^3J=6.7, ^3J=4.6 Hz, CHN in the minor isomer), 2.60 (0.37H, dddd, ^3J=12.7, ^3J=5.4, ^3J=4.6, ^4J=1.1 Hz, CHC=O *i*n the minor isomer), 1.88–2.45, 1.43–1.75 (5.63H, and 3H, respectively, two m, $CH_2CH_2CH_2CH_2$ in the both isomers and CHC=O in the major isomer), 1.35 (1.89H, d, ^3J=6.6 Hz, CH_3 *i*n the major isomer), 1.31 (1.11H, d, ^3J=6.7 Hz, CH_3 *i*n the minor isomer).

*4.2.9. 2-(2-Isothiocyanatoprop-2-yl)cyclohexanone (**6i**).* To a stirred mixture of 2-(2-methoxyprop-2-yl)cyclohexanone (**8d**) (23.77 g, 139.62 mmol) and NH_4SCN (21.76 g, 285.86 mmol) in H_2O (65 mL) was added a cooled (10–15 °C) solution of H_2SO_4 (8.15 mL, 143.02 mmol; d=1.831 g/mL, 94%) in H_2O (35 mL) in small portions (0.3–0.5 mL) over 5 min. The obtained emulsion was heated in a water bath (60 °C, temperature of bath) under intensive stirring for 3 h, and cooled. The resulting mixture was extracted with ether (75 mL, 2×50 mL). Neutralization of the combined organic layer was performed as described for compound **6b**. After neutralization the organic layer was washed with H_2O (2×50 mL), brine (2×30 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was distilled under vacuum from the flask equipped with a short-path distillation head and argon bleed tube to give compound **6i** (24.84 g, 90%) as a slightly yellow liquid in thick layer. Bp 90–104 °C/0.1 mmHg; n_D^{20}=1.5302. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 2.52 (1H, ddd, ^3J=12.5, ^3J=4.9, ^4J=1.0 Hz, CHC=O), 2.22–2.38, 1.88–2.14, 1.52–1.75 (3H, 2H, and 3H, respectively, three m, $CH_2CH_2CH_2CH_2$), 1.51 (3H, s, CH_3), 1.46 (3H, s, CH_3).

*4.2.10. 3-Isothiocyanatobutanal (**6j**).* To a cooled in an ice bath, stirred mixture of but-2-enal (**7j**) (29.89 g, 426.45 mmol) and NH_4SCN (45.77 g, 601.27 mmol) in H_2O (30 mL) under argon atmosphere was added a solution of H_2SO_4 (17.15 mL, 300.95 mmol; d=1.831 g/mL, 94%) in H_2O (18 mL) over 35 min. The resulting emulsion was stirred at room temperature for 1 h, then in a water bath (40 °C, temperature of bath) for additional 1 h, and cooled to room temperature. The mixture was extracted with ether (100 mL, 2×50 mL). Neutralization of the combined organic layer was performed as described for compound **6b**. After the neutralization was completed, the organic layer was washed with H_2O, brine, and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was distilled under vacuum from the flask equipped with a short-path distillation head and argon bleed tube to give compound **6j** (30.94 g, 56%) as a slightly yellow liquid. Bp 54–64 °C/0.1 mmHg; ^1H NMR (300.13 MHz, $CDCl_3$) δ: 9.73 (1H, dd, ^3J=1.3, ^3J=1.0 Hz, CH=O), 4.28 (1H, ddq, ^3J=7.3, ^3J=6.6, ^3J=5.7 Hz, CHN), 2.82 (1H, ddd, ^2J=17.8, ^3J=7.3, ^3J=1.3 Hz, H_A in CH_2), 2.66 (1H, ddd, ^2J=17.8, ^3J=5.7, ^3J=1.0 Hz, H_B in CH_2), 1.40 (3H, d, ^3J=6.6 Hz, CH_3).

4.3. Synthesis of 3-amino-4-hydroxyhexahydropyrimidine-2-thiones

*4.3.1. 3-Amino-4-hydroxy-4,6,6-trimethylhexahydropyrimidine-2-thione (**10a**).* Pyrimidine **10a** (3.451 g, 93%) was prepared from freshly distilled isothiocyanate **6a** (3.073 g, 19.54 mmol) and $N_2H_4 \cdot H_2O$ (1.030 g, 20.57 mmol) in EtOH (20 mL) (20 °C, 1 h) as described for compound **10c** in Method A. Mp 143.5–145.5 °C (dec, MeCN) (lit.[24] 153–154 °C). IR (Nujol) ν, cm^{-1}: 3525 (m), 3390 (br m), 3339 (m), 3221 (br vs), 3168 (m), 3140 (m), 1619 (m), 1512 (s), 1270 (s), 1195 (s); ^1H NMR (300.13 MHz, DMSO-d_6) δ: 8.17 (1H, br s, $N_{(1)}H$), 5.91 (1H, d, ^4J=1.2 Hz, OH), 4.89 (2H, br s, NH_2), 2.00 (1H, dd, ^2J=13.9, ^4J=1.7 Hz, 5-H_e), 1.89 (1H, dd, ^2J=13.9, ^4J=1.2 Hz, 5-H_a), 1.48 (3H, s, 4-CH_3), 1.28 (3H, s, 6-CH_3), 1.14 (3H, s, 6-CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 176.31 (C-3), 82.68 (C-4), 49.30 (C-6), 47.14 (C-5), 30.02 (CH_3), 28.80 (CH_3), 28.14 (CH_3).

*4.3.2. 3-Amino-4-hydroxy-4,6-dimethylhexahydropyrimidine-2-thione (**10b**) and 4-(4-oxopent-2-yl)thiosemicarbazide (**9b**).* To a cooled in an ice bath, stirred solution of freshly distilled isothiocyanate **6b** (6.588 g, 46.01 mmol) in MeCN (23 mL) was added $N_2H_4 \cdot H_2O$ (2.324 g, 46.42 mmol) dropwise over 5 min. White solid started to precipitate during the addition. The ice bath was removed and the resulting suspension was stirred at room temperature for 1 h. The solvent was removed under vacuum to a half volume and the obtained dense suspension was cooled to −18 °C. The precipitate was filtered on a cold (−18 °C) filter, rapidly washed with cold (−18 °C) MeCN (2×10 mL), cold (−18 °C) ether (2×20 mL), and dried to give product (7.485 g, 93%) as a 90:10 mixture of pyrimidine **10b** (two diastereomers, 75:25) and its acyclic isomer **9b**. After crystallization from EtOH the ratio of isomers did not change (68:22:10, respectively). Mp 119.5–122.5 °C (dec, EtOH). IR (Nujol) ν, cm^{-1}: 3276 (br vs), 3239 (br vs), 1617 (m), 1527 (s), 1485 (s), 1264 (s), 1056 (s); ^1H NMR of the major isomer of pyrimidine **10b** (300.13 MHz, DMSO-d_6) δ: 8.12 (1H, br s, $N_{(1)}H$), 6.06 (1H, d, ^4J=1.2 Hz, OH), 4.85 (2H, br s, NH_2), 3.51 (1H, ddq, ^3J=12.3, ^3J=6.4, ^3J=3.5 Hz, 6-H), 1.92 (1H, ddd, ^2J=13.2, ^3J=3.5, ^4J=2.1 Hz, 5-H_e), 1.57 (1H, ddd, ^2J=13.2, ^3J=12.3, ^4J=1.2 Hz, 5-H_a), 1.48 (3H, s, 4-CH_3), 1.08 (3H, d, ^3J=6.4 Hz, 6-CH_3); ^1H NMR of the minor isomer of pyrimidine **10b** (300.13 MHz, DMSO-d_6) δ: 7.94 (1H, br s, $N_{(1)}H$), 6.01 (1H, s, OH), 4.91 (2H, br s, NH_2), 3.38 (1H, ddq, ^3J=11.3, ^3J=6.4, ^3J=3.6 Hz, 6-H), 2.04 (1H, ddd, ^2J=13.2, ^3J=3.6, ^4J=1.8 Hz, 5-H_e), 1.73 (1H, dd, ^2J=13.2, ^3J=11.3 Hz, 5-H_a), 1.44 (3H, s, 4-CH_3), 1.10 (3H, d, ^3J=6.4 Hz, 6-CH_3); ^1H NMR of the acyclic isomer **9b** (300.13 MHz, DMSO-d_6) δ: 8.61 (1H, br s, N*H*NH_2), 7.72 (1H, br d, ^3J=8.9 Hz, NH), 4.67 (1H, dddq, ^3J=8.9, ^3J=6.9, ^3J=6.6, ^3J=5.7 Hz, CHN), 4.42 (2H, br s, NH_2), 2.78 (1H, dd, ^2J=16.3, ^3J=5.7 Hz, H_A in CH_2C=O), 2.61 (1H, dd, ^2J=16.3, ^3J=6.9 Hz, H_B in CH_2C=O), 2.10 (3H, s, CH_3C=O), 1.11 (3H, d, ^3J=6.6 Hz, CH_3); ^{13}C NMR of the major isomer of pyrimidine **10b** (75.48 MHz, DMSO-d_6) δ: 177.56 (C-2), 82.15 (C-4), 43.62 (C-5), 42.24 (C-6), 27.50 (4-CH_3), 19.86 (6-CH_3); ^{13}C NMR of the minor isomer of pyrimidine **10b** (75.48 MHz, DMSO-d_6) δ: 175.32 (C-2), 83.75 (C-4), 43.78 (C-6), 43.62 (C-5), 26.23 (4-CH_3), 20.33 (6-CH_3); ^{13}C NMR of the acyclic isomer **9b**

(75.48 MHz, DMSO-d_6) δ: 207.58 (C=O), 180.08 (C=S), 48.97 (CH_2C=O), 45.34 (CHN), 30.27 (CH_3C=O), 20.19 (CH_3CH). Anal. Calcd for $C_6H_{13}N_3OS$: C, 41.12; H, 7.48; N, 23.98. Found: C, 41.32; H, 7.47; N, 23.84.

*4.3.3. 3-Amino-4-hydroxy-4,5,6-trimethylhexahydropyrimidine-2-thione (**10c**) and 4-(3-methyl-4-oxopent-2-yl)thiosemicarbazide (**9c**). Method A*: To a cooled in an ice bath, stirred solution of freshly distilled isothiocyanate **6c** (10.112 g, 64.36 mmol) in MeCN (50 mL) was added $N_2H_4 \cdot H_2O$ (3.242 g, 64.76 mmol) dropwise over 5 min. White solid started to precipitate during the addition. The ice bath was removed and the resulting suspension was stirred at room temperature for 1 h. The solvent was removed under vacuum, the residue was triturated with ether until crystallization was complete, the obtained suspension was cooled (−18 °C). The precipitate was filtered, washed with cold ether (4×25 mL), and dried to give product (11.079 g, 91%) as a 89:11 mixture of pyrimidine **10c** (four diastereomers, 45:26:18:11) and its acyclic isomer **9c** (two diastereomers, 78:22).

Method B: This product (0.791 g, 90%) as a 89:11 mixture of pyrimidine **10c** (four diastereomers, 46:26:19:9) and its acyclic isomer **9c** (two diastereomers, 78:22) was prepared from freshly distilled isothiocyanate **6c** (0.730 g, 4.64 mmol) and $N_2H_4 \cdot H_2O$ (0.248 g, 4.95 mmol) in EtOH (5 mL) (20 °C, 1 h) as described in Method A. The analytically pure sample (0.136 g) as a 89:11 mixture of pyrimidine **10c** (four diastereomers, 46:24:17:12) and its acyclic isomer **9c** (two diastereomers, 80:20) was obtained from 0.356 g of the crude product using crystallization from MeCN (3 mL) in the presence of DBU (0.070 mL). (*Note*: crystallization from MeCN or EtOH without DBU led to partial dehydration of the product). Mp 109.5–113.5 °C (dec, MeCN). IR (Nujol) ν, cm^{-1}: 3327 (s), 3311 (s), 3288 (s), 3252 (s), 3230 (s), 3136 (s), 1620 (m), 1523 (s), 1495 (s), 1256 (s), 1041 (s); ^{1}H NMR of the major isomer (46%) of pyrimidine **10c** (300.13 MHz, DMSO-d_6) δ: 7.98 (1H, br d, ^4J=1.8 Hz, $N_{(1)}H$), 6.16 (1H, s, OH), 4.89 (2H, br s, NH_2), 3.85 (1H, ddq, ^3J=6.9, ^3J=3.5, ^4J=0.8 Hz, 6-H), 1.67 (1H, ddq, ^3J=7.0, ^3J=3.5, ^4J=1.8 Hz, 5-H), 1.47 (3H, s, 4-CH_3), 1.02 (3H, d, ^3J=6.9 Hz, 6-CH_3), 0.71 (3H, d, ^3J=7.0 Hz, 5-CH_3); ^{1}H NMR of the first minor isomer (26%) of pyrimidine **10c** (300.13 MHz, DMSO-d_6) δ: 8.09 (1H, br s, $N_{(1)}H$), 5.89 (1H, d, ^4J=0.9 Hz, OH), 4.90 (2H, br s, NH_2), 3.10 (1H, dq, ^3J=11.0, ^3J=6.5 Hz, 6-H), 1.48 (1H, ddq, ^3J=11.0, ^3J=6.7, ^4J=0.9 Hz, 5-H), 1.48 (3H, s, 4-CH_3), 1.09 (3H, d, ^3J=6.5 Hz, 6-CH_3), 0.90 (3H, d, ^3J=6.7 Hz, 5-CH_3); ^{1}H NMR of the second minor isomer (19%) of pyrimidine **10c** (300.13 MHz, DMSO-d_6) δ: 7.86 (1H, br s, $N_{(1)}H$), 5.97 (1H, s, OH), 4.97 (2H, br s, NH_2), 3.06 (1H, dq, ^3J=10.8, ^3J=6.5 Hz, 6-H), 1.70 (1H, dq, ^3J=10.8, ^3J=6.9 Hz, 5-H), 1.26 (3H, s, 4-CH_3), 1.09 (3H, d, ^3J=6.5 Hz, 6-CH_3, signals overlap with signals of the 6-CH_3 group of the major isomer), 0.91 (3H, d, ^3J=6.9 Hz, 5-CH_3); ^{1}H NMR of the third minor isomer (9%) of pyrimidine **10c** (300.13 MHz, DMSO-d_6) δ: 7.95 (1H, br s, $N_{(1)}H$), 5.95 (1H, br s, OH), 4.88 (2H, br s, NH_2), 3.49 (1H, ddq, ^3J=6.7, ^3J=4.1, ^4J=1.9 Hz, 4-H), 1.90 (1H, ddq, ^3J=6.9, ^3J=4.1, ^4J=1.0 Hz, 5-H), 1.47 (3H, s, 4-CH_3, signal partly overlaps with signal of the 4-CH_3 group of the major isomer), 1.06 (3H, d, ^3J=6.7 Hz, 6-CH_3), 0.88 (3H, d, ^3J=6.9 Hz, 5-CH_3); ^{1}H NMR of the major isomer of thiosemicarbazide **9c** (300.13 MHz, DMSO-d_6) δ: 8.67 (1H, br s, N*H*NH_2), 7.65 (1H, br d, ^3J=9.5 Hz, N*H*CH), 4.69 (1H, ddq, ^3J=9.5, ^3J=7.0, ^3J=6.6 Hz, CHN), 4.47 (2H, br s, NH_2), 2.82 (1H, dq, ^3J=7.0, ^3J=7.0 Hz, CHC=O), 2.14 (3H, s, CH_3C=O), 1.05 (3H, d, ^3J=6.6 Hz, C*H*$_3$CHC=O), 0.99 (3H, d, ^3J=7.0 Hz, C*H*$_3$CHN); ^{1}H NMR of the minor isomer of thiosemicarbazide **9c** (300.13 MHz, DMSO-d_6) δ: 8.69 (1H, br s, N*H*NH_2), 4.53–4.65 (1H, m, CHN), 2.95 (1H, dq, ^3J=7.1, ^3J=5.5 Hz, CHC=O), 2.15 (3H, s, CH_3C=O), 0.97 (3H, d, ^3J=7.1 Hz, C*H*$_3$CHN), signals of other protons overlap with proton signals of the other isomers; ^{13}C NMR of the major isomer (46%) of pyrimidine **10c** (75.48 MHz, DMSO-d_6) δ: 176.97 (C-2), 85.43 (C-4), 44.72 (C-6), 41.51 (C-5), 25.60 (4-CH_3), 16.34 (6-CH_3), 8.21 (5-CH_3); ^{13}C NMR of the first minor isomer (26%) of pyrimidine **10c** (75.48 MHz, DMSO-d_6) δ: 177.04 (C-2), 84.92 (C-4), 47.43 (C-6), 43.82 (C-5), 24.28 (4-CH_3), 18.42 (6-CH_3), 11.86 (5-CH_3); ^{13}C NMR of the second minor isomer (19%) of pyrimidine **10c** (75.48 MHz, DMSO-d_6) δ: 174.15 (C-2), 86.58 (C-4), 49.17 (C-6), 44.23 (C-5), 20.00 (4-CH_3), 18.73 (6-CH_3), 11.66 (5-CH_3); ^{13}C NMR of the third minor isomer (9%) of pyrimidine **10c** (75.48 MHz, DMSO-d_6) δ: 175.39 (C-2), 85.79 (C-4), 47.37 (C-6), 40.46 (C-5), 26.59 (4-CH_3), 16.72 (6-CH_3), 8.54 (5-CH_3); ^{13}C NMR of the major isomer of thiosemicarbazide **9c** (75.48 MHz, DMSO-d_6) δ: 210.74 (C=O), 50.91 (CHN), 49.87 (*C*HC=O), 29.29 (CH_3C=O), 18.55 (CH_3CHN), 12.65 (CH_3CHC=O), signal of the C=S carbon was not detected in the spectrum. Anal. Calcd for $C_7H_{15}N_3OS$: C, 44.42; H, 7.99; N, 22.20. Found: C, 44.47; H, 8.22; N, 22.08.

*4.3.4. 1-Amino-7a-hydroxy-4-methyloctahydro-2H-cyclopenta[d]pyrimidine-2-thione (**10d**) and 4-[1-(2-oxocyclopentyl)ethyl]thiosemicarbazide (**9d**).* This product (2.089 g, 82%) as a 97:3 mixture of pyrimidine **10d** (four diastereomers, 71:26:2:1) and its acyclic isomer **9d** (a single diastereomer) was prepared from 2.331 g of freshly distilled isothiocyanate **6d** (88 mol % in a mixture with **7d**; 2.141 g, 12.64 mmol) and $N_2H_4 \cdot H_2O$ (0.633 g, 12.64 mmol) in MeCN (10 mL) (20 °C, 1 h 30 min) as described for compound **10c** in Method A. The analytically pure sample (0.099 g) as a 96:4 mixture of pyrimidine **10d** (two diastereomers, 96:0:0:4, respectively) and its acyclic isomer **9d** (a single diastereomer) was obtained from 0.304 g of the crude product after crystallization from MeCN (3 mL) in the presence of DBU (0.058 mL). (*Note*: crystallization from MeCN without DBU led to partial dehydration of the product). Mp 146–147.5 °C (dec, MeCN). IR (Nujol) ν, cm^{-1}: 3296 (br s), 3231 (br s), 3147 (s), 1603 (s), 1496 (s), 1230 (s), 1093 (s), 1050 (s); ^{1}H NMR of the major isomer (71%) of pyrimidine **10d** (300.13 MHz, DMSO-d_6) δ: 8.10 (1H, br s, $N_{(3)}H$), 6.20 (1H, s, OH), 4.95 (2H, br s, NH_2), 3.52 (1H, dq, ^3J=6.7, ^3J=3.5 Hz, 4-H), 2.07 (1H, ddt, $^3J_1$+$^3J_2$=18.5, ^3J=3.5, ^4J=1.8 Hz, 4a-H), 2.37–2.53, 1.48–1.72, and 1.19–1.41 (1H, 3H, and 2H, respectively, three m, 5-H, 6-H, and 7-H), 1.02 (3H, d, ^3J=6.7 Hz, CH_3); ^{1}H NMR of the first minor isomer (26%) of pyrimidine **10d** (300.13 MHz, DMSO-d_6) δ: 8.10 (1H, br s, $N_{(3)}H$), 5.93 (1H, s, OH), 4.93 (2H, br s, NH_2), 3.31–3.41 (1H, m, 4-H, signals partly overlap with signal of HOD in solvent), 1.08 (3H, d, ^3J=6.5 Hz, CH_3), signals of other protons overlap with proton signals of the other isomers; ^{1}H NMR of the second minor isomer (2%) of pyrimidine **10d** (300.13 MHz, DMSO-d_6) δ: 8.35 (1H, br d, ^3J=3.6 Hz, $N_{(3)}H$), 5.76 (1H, d, ^4J=1.4 Hz, OH), 1.18 (3H, d, ^3J=6.9 Hz, CH_3), signals of other protons overlap with proton signals of the other isomers; ^{1}H NMR of the third minor isomer (1%) of pyrimidine **10d** (300.13 MHz, DMSO-d_6) δ: 8.31 (1H, br s, $N_{(3)}H$), 5.79 (1H, s, OH), 4.91 (2H, br s, NH_2), 2.85 (1H, ddq, ^3J=9.9, ^3J=6.6, ^3J=1.3 Hz, 4-H), 1.08 (3H, d, ^3J=6.6 Hz, CH_3), signals of other protons overlap with proton signals of the other isomers; ^{1}H NMR of the acyclic isomer **9d** (300.13 MHz, DMSO-d_6) δ: 8.66 (1H, br s, N*H*NH_2), 4.51 (1H, ddq, ^3J=9.2, ^3J=6.5, ^3J=6.5 Hz, CHN), 4.47 (2H, br s, NH_2), 1.08 (3H, d, ^3J=6.5 Hz, CH_3), signals of other protons overlap with proton signals of the cyclic isomers; ^{13}C NMR of the major isomer (71%) of pyrimidine **10d** (75.48 MHz, DMSO-d_6) δ: 177.04 (C-2), 92.90 (C-7a), 48.84 (C-4), 43.28 (C-4a), 36.01 (CH_2), 21.24 (CH_2), 19.47 (CH_2), 17.27 (CH_3). Anal. Calcd for $C_8H_{15}N_3OS$: C, 47.74; H, 7.51; N, 20.88. Found: C, 47.79; H, 7.47; N, 20.85.

*4.3.5. 1-Amino-7a-hydroxy-4,4-dimethyloctahydro-2H-cyclopenta[d]pyrimidine-2-thione (**10e**).* This product (10.487 g, 96%) as a mixture of two isomers in a ratio of 60:40 was prepared from 10.024 g of freshly distilled isothiocyanate **6e** (92 mol % in a mixture with **7e**; 9.466 g, 51.65 mmol) and $N_2H_4 \cdot H_2O$ (2.539 g, 50.73 mmol) in MeCN (50 mL) (20 °C, 2 h 5 min) as described for compound **10c** in Method A. After crystallization from EtOH the diastereomeric

ratio changed to 93:7, respectively. Mp 146–148 °C (dec, EtOH) (rate of heating was more than 1 °C/10–20 s), Mp 176.5–178 °C (dec, EtOH) (rate of heating was 1 °C/1 min). IR (Nujol) ν, cm^{-1}: 3303 (sh), 3288 (s), 3223 (br s), 3144 (m), 3023 (m), 1610 (m), 1531 (s), 1216 (s), 1077 (s), 1054 (m); ^{1}H NMR of the 60:40 diastereomeric mixture (300.13 MHz, DMSO-d_6) δ: 8.22 (0.6H, br s, $N_{(3)}$H in the major isomer), 8.09 (0.4H, br s, $N_{(3)}$H in the minor isomer), 6.07 (0.4H, s, OH in the minor isomer), 5.81 (0.6H, d, ^4J=1.3 Hz, OH in the major isomer), 4.97 (0.8H, br s, NH_2 in the minor isomer), 4.92 (1.2H, br s, NH_2 in the major isomer), 1.28–2.31 (7H, m, 4a-H, 5-H, 6-H, 7-H in the both isomers), 1.25 (1.2H, s, 4-CH_3 in the minor isomer), 1.24 (1.8H, s, 4-CH_3 in the major isomer), 1.15 (1.8H, s, 4-CH_3 in the major isomer), 1.04 (1.2H, s, 4-CH_3 in the minor isomer); ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 178.24 (C-2), 88.89 (C-7a), 54.42 (C-4), 52.25 (C-4a), 36.88 (CH_2), 30.85 (4-CH_3), 23.22 (4-CH_3), 22.44 (CH_2), 19.58 (CH_2); ^{13}C NMR of the minor isomer (75.48 MHz, DMSO-d_6) δ: 176.52 (C-2), 93.06 (C-7a), 52.93 (C-4a), 50.88 (C-4), 38.71 (CH_2), 27.40 (4-CH_3), 25.91 (CH_2), 25.85 (4-CH_3), 19.96 (CH_2). Anal. Calcd for $C_9H_{17}N_3OS$: C, 50.20; H, 7.96; N, 19.52. Found: C, 50.37; H, 8.35; N, 19.12.

*4.3.6. 1′-Amino-7a′-hydroxyhexahydrospiro[cyclopentane-1,4′-cyclopenta[d]pyrimidine]-2′(3′H)-thione (**10f**).* To a cooled in an ice bath, stirred solution of freshly distilled isothiocyanate **6f** (8.400 g, 79 mol % in a mixture with **7f**; 7.054 g, 33.70 mmol) in MeCN (30 mL) was added $N_2H_4\cdot H_2O$ (1.808 g, 36.12 mmol) dropwise over 3 min. White solid started to precipitate during the addition. The resulting suspension was stirred in an ice bath for 10 min, and cooled to −18 °C. The precipitate was filtered on a cold (−18 °C) filter, rapidly washed with cold (−18 °C) MeCN (10 mL), cold (−18 °C) ether (3×20 mL), and dried to give compound **10f** (7.548 g, 93%) as a mixture of two isomers in a ratio of 60:40. After crystallization from MeCN the diastereomeric ratio did not change. Mp 125–126.5 °C (dec, MeCN); IR (Nujol) ν, cm^{-1}: 3280 (br s), 3209 (br s), 3162 (m), 1614 (m), 1517 (s), 1247 (s), 1200 (s); ^{1}H NMR of the 61:39 diastereomeric mixture (300.13 MHz, DMSO-d_6) δ: 8.23 (1H, br s, $N_{(3)}$H in both isomers), 6.02 (0.61H, s, OH in the major isomer), 5.73 (0.39H, d, ^4J=1.3 Hz, OH in the minor isomer), 4.97 (1.22H, br s, NH_2 in the major isomer), 4.92 (0.78H, br s, NH_2 in the minor isomer), 2.07–2.36, 1.22–1.99 (2H, and 13H, respectively, two m, 4a-H, 5-H, 6-H, 7-H, and $CH_2CH_2CH_2CH_2$ in both isomers); ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 176.51 (C-2), 93.49 (C-7a), 61.73 (C-4), 51.79 (C-4a), 38.03 (CH_2), 37.38 (CH_2), 35.58 (CH_2), 25.89 (CH_2), 23.56 (CH_2), 22.28 (CH_2), 20.14 (CH_2); ^{13}C NMR of the minor isomer (75.48 MHz, DMSO-d_6) δ: 177.67 (C-2), 88.84 (C-7a), 64.36 (C-4), 51.21 (C-4a), 40.26 (CH_2), 36.63 (CH_2), 33.77 (CH_2), 24.99 (CH_2), 23.07 (CH_2), 23.04 (CH_2), 19.75 (CH_2). Anal. Calcd for $C_{11}H_{19}N_3OS$: C, 54.74; H, 7.93; N, 17.41. Found: C, 54.82; H, 8.15; N, 17.61.

*4.3.7. 3-Amino-4-hydroxy-4-methyldecahydroquinazoline-2-thione (**10g**) and 4-(2-acetylcyclohexyl)thiosemicarbazide (**9g**).* To a cooled in an ice bath, stirred solution of freshly distilled isothiocyanate **6g** (7.022 g, 38.32 mmol) in MeCN (19 mL) was added $N_2H_4\cdot H_2O$ (2.015 g, 40.24 mmol) dropwise over 5 min. White solid started to precipitate during the addition. The resulting suspension was stirred at room temperature for 1 h, and cooled to −18 °C. The precipitate was filtered on a cold (−18 °C) filter, rapidly washed with cold (−18 °C) MeCN (3×10 mL), and dried to give product (7.225 g, 88%) as a 97:3 mixture of pyrimidine **10g** (four diastereomers, 50:29:13:8) and its acyclic isomer **9g** (two diastereomers, 56:44). Crystallization from MeCN gave the analytically pure sample as a 97:3 mixture of pyrimidine **10g** (four diastereomers, 32:42:20:6, respectively) and its acyclic isomer **9g** (two diastereomers, 27:73, respectively). Mp 127–140 °C (dec, MeCN); IR (Nujol) ν, cm^{-1}: 3232 (br vs), 3123 (m), 1598 (m), 1545 (s), 1530 (s), 1258 (s), 1097 (s), 1080 (s), 1065 (s), 1049 (s); ^{1}H NMR of the major isomer (50%) of pyrimidine **10g** (300.13 MHz, DMSO-d_6) δ: 8.02 (1H, br d, ^3J=1.7 Hz, $N_{(1)}$H), 6.09 (1H, s, OH), 4.88 (2H, br s, NH_2), 3.76–3.81 (1H, m, 8a-H), 1.42 (3H, s, CH_3), 0.81–2.06 (9H, m, 4a-H, 5-H, 6-H, 7-H, and 8-H); ^{1}H NMR of the first minor isomer (29%) of pyrimidine **10g** (300.13 MHz, DMSO-d_6) δ: 8.15 (1H, br s, $N_{(1)}$H), 5.92 (1H, d, ^4J=0.8 Hz, OH), 4.89 (2H, br s, NH_2), 3.02 (1H, ddd, ^3J=11.0, ^3J=11.0, ^3J=4.1 Hz, 8a-H), 1.46 (3H, s, CH_3), 0.96–2.06 (9H, m, 4a-H, 5-H, 6-H, 7-H, and 8-H, signals overlap with proton signals of the other isomers); ^{1}H NMR of the second minor isomer (13%) of pyrimidine **10g** (300.13 MHz, DMSO-d_6) δ: 7.91 (1H, br s, $N_{(1)}$H), 5.96 (1H, s, OH), 4.95 (2H, br s, NH_2), 2.94 (1H, ddd, ^3J=11.0, ^3J=11.0, ^3J=4.0 Hz, 8a-H), 1.29 (3H, s, CH_3), 0.96–2.06 (9H, m, 4a-H, 5-H, 6-H, 7-H, and 8-H, signals overlap with proton signals of the other isomers); ^{1}H NMR of the third minor isomer (8%) of pyrimidine **10g** (300.13 MHz, DMSO-d_6) δ: 7.79 (1H, br s, $N_{(1)}$H), 5.94 (1H, s, OH), 3.61–3.66 (1H, m, 8a-H), 1.44 (3H, s, CH_3), signals of other protons overlap with proton signals of the other isomers; ^{1}H NMR of the major isomer (56%) of thiosemicarbazide **9g** (300.13 MHz, DMSO-d_6) δ: 8.75 (1H, br s, N*H*NH_2), 4.49 (2H, br s, NH_2), 2.83 (1H, ddd, ^3J=6.7, ^3J=6.7, ^3J=4.0 Hz, CHC═O), 2.12 (3H, s, CH_3), signals of other protons overlap with proton signals of the cyclic isomers; ^{1}H NMR of the minor isomer (44%) of thiosemicarbazide **9g** (300.13 MHz, DMSO-d_6) δ: 8.61 (1H, br s, N*H*NH_2), 7.66 (1H, br d, ^3J=8.9 Hz, N*H*CH), 4.43 (2H, br s, NH_2), 2.64 (1H, ddd, ^3J=10.5, ^3J=10.5, ^3J=3.8 Hz, CHC═O), 2.10 (3H, s, CH_3), signals of other protons overlap with proton signals of the cyclic isomers; ^{13}C NMR of the major isomer (50%) of pyrimidine **10g** (75.48 MHz, DMSO-d_6) δ: 177.38 (C-2), 84.67 (C-4), 45.15 (C-8a), 43.35 (C-4a), 27.89 (CH_2), 25.10 (CH_3), 24.11 (CH_2), 22.23 (CH_2), 19.39 (CH_2); ^{13}C NMR of the first minor isomer (29%) of pyrimidine **10g** (75.48 MHz, DMSO-d_6) δ: 176.88 (C-2), 84.51 (C-4), 49.46 (C-8a), 47.00 (C-4a), 30.88 (CH_2), 24.76 (CH_2), 24.50 (CH_2), 23.64 (CH_3), 23.46 (CH_2); ^{13}C NMR of the second minor isomer (13%) of pyrimidine **10g** (75.48 MHz, DMSO-d_6) δ: 174.38 (C-2), 86.15 (C-4), 50.79 (C-8a), 47.80 (C-4a), 31.42 (CH_2), 24.87 (CH_2), 24.41 (CH_2), 23.50 (CH_2), 20.88 (CH_3); ^{13}C NMR of the third minor isomer (8%) of pyrimidine **10g** (75.48 MHz, DMSO-d_6) δ: 174.03 (C-2), 85.50 (C-4), 47.11 (C-8a), 42.83 (C-4a), 28.47 (CH_2), 28.41 (CH_2), 26.66 (CH_3), 20.64 (CH_2), 19.47 (CH_2). Anal. Calcd for $C_9H_{17}N_3OS$: C, 50.20; H, 7.96; N, 19.52. Found: C, 50.32; H, 7.80; N, 19.51.

*4.3.8. 1-Amino-8a-hydroxy-4-methyldecahydroquinazoline-2-thione (**10h**).* Pyrimidine **10h** (4.576 g, 96%) as a mixture of four isomers in a ratio of 36:35:27:2 was prepared from 4.159 g of freshly distilled isothiocyanate **6h** (97 mol % in a mixture with **7h**; 4.074 g, 22.23 mmol) and $N_2H_4\cdot H_2O$ (1.163 g, 23.23 mmol) in MeCN (21 mL) (20 °C, 2 h 20 min) as described for compound **10c** in Method A. The analytically pure sample (0.158 g) as a mixture of three isomers in a ratio of 0:53:42:5, respectively, was obtained from 0.398 g of the crude **10h** after crystallization from MeCN (3.6 mL) in the presence of DBU (0.070 mL). (*Note*: crystallization from MeCN or EtOH without DBU led to partial formation of the dehydration products). Mp 139.5–145 °C (dec, MeCN). IR (Nujol) ν, cm^{-1}: 3303 (br s), 3237 (m), 3142 (s), 1625 (m), 1530 (s), 1489 (s), 1258 (s), 1071 (s), 1028 (s); ^{1}H NMR of the major isomer (36%) (300.13 MHz, DMSO-d_6) δ: 8.34 (1H, br d, ^3J=3.8 Hz, $N_{(3)}$H), 5.71 (1H, d, ^4J=1.6 Hz, OH), 4.82 (2H, br s, NH_2), 3.23 (1H, ddq, ^3J=6.8, ^3J=6.2, ^3J=3.8 Hz, 4-H), 2.33–2.41 (1H, m, 8-H_{eq}), 1.83–1.92 (1H, m, 8-H_{ax}), 1.10–1.71 (6H, m, 5-H, 6-H, 7-H, signals overlap with proton signals of the other isomers), 1.13 (3H, d, ^3J=6.8 Hz, CH_3); ^{1}H NMR of the first minor isomer (35%) (300.13 MHz, DMSO-d_6) δ: 8.08 (1H, br s, $N_{(3)}$H), 5.88 (1H, d, ^4J=1.2 Hz, OH), 4.83 (2H, br s, NH_2), 3.17 (1H, dq, ^3J=10.9, ^3J=6.4 Hz, 4-H), 2.39–2.48 (1H, m, 8-H_{eq}), 1.10–1.71 (7H, m, 8-H_{ax}, 5-H, 6-H, 7-H, signals overlap with proton signals of the other isomers), 1.06 (3H, d, ^3J=6.4 Hz, CH_3); ^{1}H NMR of the second minor isomer (27%) (300.13 MHz, DMSO-d_6) δ: 8.07 (1H, br s, $N_{(3)}$H), 6.04 (1H, s, OH),

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4.77 (2H, br s, NH_2), 3.86 (1H, dq, ^3J=6.9, ^3J=3.3 Hz, 4-H), 2.60–2.68 (1H, m, 8-H_{eq}), 0.76–1.71 (7H, m, 8-H_{ax}, 5-H, 6-H, 7-H, signals overlap with proton signals of the other isomers), 1.00 (3H, d, ^3J=6.9 Hz, CH_3); ^{1}H NMR of the third minor isomer (2%) (300.13 MHz, DMSO-d_6) δ: 8.02 (1H, br s, $N_{(3)}H$), 5.48 (1H, s, OH), 4.85 (2H, br s, NH_2), signals of other protons overlap with proton signals of the other isomers; ^{13}C NMR of the major isomer (36%) (75.48 MHz, DMSO-d_6) δ: 176.59 (C-2), 83.84 (C-8a), 48.57 (C-4), 42.36 (C-4a), 36.06 (CH_2), 24.78 (CH_2), 24.18 (CH_2), 21.69 (CH_2), 17.29 (4-CH_3); ^{13}C NMR of two minor isomers (35 and 27%) (75.48 MHz, DMSO-d_6) δ: 178.43, 177.45 (C-2), 84.24, 82.62 (C-8a), 46.96, 46.64 (C-4), 44.10, 43.70 (C-4a), 36.37, 34.50, 24.20, 24.11, 23.61, 22.36, 21.52, 21.06 ($CH_2CH_2CH_2CH_2$), 17.99, 15.71 (4-CH_3). Anal. Calcd for $C_9H_{17}N_3OS$: C, 50.20; H, 7.96; N, 19.52. Found: C, 50.28; H, 7.99; N, 19.47.

*4.3.9. 1-Amino-8a-hydroxy-4,4-dimethyldecahydroquinazoline-2-thione (**10i**).* Pyrimidine **10i** (5.163 g, 97%) as a mixture of two isomers in a ratio of 84:16 was prepared from freshly distilled isothiocyanate **6i** (4.603 g, 23.33 mmol) and $N_2H_4\cdot H_2O$ (1.196 g, 23.90 mmol) in MeCN (20 mL) (20 °C, 2 h) as described for compound **10c** in Method A. After crystallization from EtOH the diastereomeric ratio changed to 95:5, respectively. Mp 188–188.5 °C (dec, EtOH). IR (Nujol) ν, cm^{-1}: 3326 (m), 3231 (br s), 3029 (m), 1624 (m), 1535 (s), 1286 (s), 1216 (s); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.17 (1H, br s, $N_{(3)}H$), 5.74 (1H, d, ^4J=1.5 Hz, OH), 4.83 (2H, br s, NH_2), 2.37–2.45 (1H, m, 8-H_{eq}), 1.09–1.74 (8H, m, 4a-H, 5-H, 6-H, 7-H, 8-H_{ax}), 1.17 (3H, s, 4-CH_3), 1.13 (3H, s, 4-CH_3); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 8.13 (1H, br s, $N_{(3)}H$), 5.76 (1H, s, OH), 4.78 (2H, br s, NH_2), 2.50–2.59 (1H, m, 8-H_{eq}, signals partly overlap with proton signals of the solvent), 1.46 (3H, s, 4-CH_3), 1.08 (3H, s, 4-CH_3), signals of other protons overlap with protons signals of the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 176.31 (C-2), 83.44 (C-8a), 52.96 (C-4), 49.14 (C-4a), 36.26 (CH_2), 29.53 (4-CH_3), 24.93 (CH_2), 23.71 (4-CH_3), 22.36 (CH_2), 21.81 (CH_2). Anal. Calcd for $C_{10}H_{19}N_3OS$: C, 52.37; H, 8.35; N, 18.32. Found: C, 52.31; H, 8.54; N, 18.24.

*4.3.10. 3-Amino-4-hydroxy-6-methylhexahydropyrimidine-2-thione (**10j**).* To a cooled in an ice bath, stirred solution of isothiocyanate **6j** (8.581 g, 66.43 mmol) in EtOH (50 mL) was added $N_2H_4\cdot H_2O$ (3.360 g, 67.11 mmol) dropwise over 5 min. White solid started to precipitate during the addition. The ice bath was removed and the resulting suspension was stirred for 1 h at room temperature. The obtained suspension was cooled to −18 °C. The precipitate was filtered on a cold (−18 °C) filter, rapidly washed with cold (−18 °C) EtOH (3×20 mL), cold (−18 °C) ether (2×20 mL), and dried to give pyrimidine **10j** (7.977 g, 74%) as a mixture of two diastereomers in a ratio of 90:10. After crystallization from EtOH the ratio of isomers did not change. Mp 143.5–144 °C (dec, EtOH). IR (Nujol) ν, cm^{-1}: 3234 (br vs), 1622 (m), 1604 (m), 1531 (s), 1502 (m), 1486 (m), 1265 (s), 1037 (s); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.14 (1H, br s, $N_{(1)}H$), 6.39 (1H, dd, ^3J=4.8, ^4J=1.0 Hz, OH), 5.15 (2H, br s, NH_2), 4.88 (1H, ddd, ^3J=4.8, ^3J=3.4, ^3J=2.2 Hz, 4-H), 3.49 (1H, ddq, ^3J=12.2, ^3J=6.4, ^3J=3.5 Hz, 6-H), 1.84 (1H, dddd, ^2J=13.3, ^3J=3.5, ^3J=2.2, ^4J=2.0 Hz, 5-H_e), 1.52 (1H, dddd, ^2J=13.3, ^3J=12.2, ^3J=3.4, ^4J=1.0 Hz, 5-H_a), 1.11 (3H, d, ^3J=6.4 Hz, CH_3); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 8.06 (1H, br s, $N_{(1)}H$), 6.36 (1H, d, ^3J=5.5 Hz, OH), 5.13 (2H, br s, NH_2), 4.94 (1H, ddd, ^3J=6.3, ^3J=5.5, ^3J=5.1 Hz, 4-H), 2.11 (1H, dddd, ^2J=13.5, ^3J=5.1, ^3J=4.4, ^4J=1.0 Hz, 5-H_e), 1.68 (1H, ddd, ^2J=13.5, ^3J=7.8, ^3J=6.3 Hz, 5-H_a), 1.14 (3H, d, ^3J=6.5 Hz, CH_3), signals of the 6-H proton completely overlap with signals of the analogous proton of the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 176.57 (C-2), 78.35 (C-4), 41.89 (C-6), 36.65 (C-5), 19.83 (CH_3). Anal. Calcd for $C_5H_{11}N_3OS$: C, 37.25; H, 6.88; N, 26.06. Found: C, 37.62; H, 7.18; N, 25.80.

4.4. Synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones

*4.4.1. 5,5,7-Trimethyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-thione (**11a**). Method A*: To a cooled in an ice bath, stirred emulsion of isothiocyanate **6a** (34.80 g, 221.32 mmol) in H_2O (240 mL) was added a solution of NaOH (6.04 g, 151.00 mmol) and $N_2H_4\cdot H_2O$ (12.25 g, 244.71 mmol) in H_2O (60 mL) over 18 min, then the ice bath was removed. After addition the starting isothiocyanate almost dissolved and the solid material started to precipitate in 5 min. The resulting suspension was stirred at room temperature for 1.5 h, cooled in an ice bath for 2 min, and then AcOH (8.75 mL, 152.88 mmol) was gradually added. The mixture was stirred for additional 2 min and cooled. The precipitate was filtered, washed with ice cold H_2O (6×75 mL), petroleum ether (2×50 mL), cold ether (4×50 mL), and dried to give triazepine **11a** (28.28 g, 75%).

Method B: Triazepine **11a** (0.872 g, 93%) was prepared from pyrimidine **10a** (1.035 g, 5.47 mmol) and NaOH (0.161 g, 4.03 mmol) in H_2O (7 mL) (rt, 1 h 20 min) as described for compound **11b** in Method B. Mp 213–213.5 °C (dec, EtOH) (lit.[5e] 209–210 °C). IR (Nujol) ν, cm^{-1}: 3264 (s), 3220 (br vs), 3097 (w), 1674 (m), 1561 (s), 1191 (s); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.13 (1H, br d, ^4J=2.0 Hz, $N_{(2)}H$), 8.24 (1H, unresolved br d, $N_{(4)}H$), 2.55 (2H, d, ^4J=0.8 Hz, 6-H), 1.99 (3H, s, 7-CH_3), 1.21 (6H, s, 5-CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 175.32 (C-3), 161.53 (C-7), 57.64 (C-5), 44.38 (C-6), 29.71 (5-CH_3), 25.43 (7-CH_3); MS (EI) *m/z* 173 [3, $(M+2)^+$], 172 [8, $(M+1)^+$], 171 (59, M^+), 156 (1), 117 (3), 116 (12), 115 (100), 100 (60), 97 (32), 89 (13), 83 (12), 72 (24), 60 (15), 59 (16), 58 (14), 57 (16), 56 (32), 55 (15), 42 (18), 41 (24), 39 (11), 28 (10).

*4.4.2. 5,7-Dimethyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-thione (**11b**). Method A*: To a cooled in an ice bath, stirred emulsion of isothiocyanate **6b** (0.453 g, 3.16 mmol) in H_2O (3 mL) was added a solution of NaOH (0.095 g, 2.37 mmol) and $N_2H_4\cdot H_2O$ (0.162 g, 3.24 mmol) in H_2O (1 mL) over 1 min, then the ice bath was removed. After addition the starting isothiocyanate almost dissolved and the solid material started to precipitate in 5 min. The resulting suspension was stirred at room temperature for 3 h, then AcOH (0.140 mL, 2.45 mmol) and saturated aqueous $NaHCO_3$ (1 mL) were subsequently added, and the suspension was cooled. The precipitate was filtered, washed with cold H_2O, petroleum ether, and dried to give triazepine **11b** (0.306 g, 61%).

Method B: To a stirred solution of NaOH (0.191 g, 4.78 mmol) in H_2O (7 mL) was added pyrimidine **10b** (1.122 g, 6.40 mmol), the resulting suspension was stirred at room temperature for 3 h, then AcOH (0.280 mL, 4.89 mmol) and saturated aqueous $NaHCO_3$ (1 mL) were subsequently added, and the suspension was cooled. The precipitate was filtered, washed with cold H_2O, petroleum ether, and dried to give triazepine **11b** (0.837 g, 83%). Mp 198 °C (dec, EtOH). IR (Nujol) ν, cm^{-1}: 3222 (br s), 3176 (br s), 3134 (br s), 3014 (m), 1667 (m), 1576 (m), 1557 (w), 1490 (s), 1210 (s); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.11 (1H, br d, ^4J=2.1 Hz, $N_{(2)}H$), 8.43 (1H, br dd, ^3J=3.5, ^4J=2.1 Hz, $N_{(4)}H$), 3.62 (1H, dddq, ^3J=7.0, ^3J=6.5, ^3J=3.5, ^3J=2.7 Hz, 5-H), 2.58 (1H, dd, ^2J=14.6, ^3J=2.7 Hz, 6-H_A), 2.49 (1H, dd, ^2J=14.6, ^3J=7.0 Hz, 6-H_B), 1.96 (3H, s, 7-CH_3), 1.13 (3H, d, ^3J=6.5 Hz, 5-CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 176.42 (C-3), 161.04 (C-7), 50.74 (C-5), 39.61 (C-6), 25.13 (7-CH_3), 22.22 (5-CH_3); MS (EI) *m/z* 159 [4, $(M+2)^+$], 158 [9, $(M+1)^+$], 157 (100, M^+), 142 (2), 124 (4), 115 (13), 101 (8), 97 (11), 99 (35), 89 (15), 86 (57), 83 (36), 82 (18), 81 (9), 74 (10), 72 (23), 71 (84), 69 (21), 68 (9), 67 (13), 60 (64), 59 (52), 57 (38), 56 (75), 54 (23), 53 (21), 44 (27), 43 (27), 42 (75), 41 (83), 39 (46), 30 (13), 29 (11), 28 (30), 27 (19). Anal. Calcd for $C_6H_{11}N_3S$: C, 45.83; H, 7.05; N, 26.72. Found: C, 45.72; H, 7.17; N, 26.75.

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*4.4.3. 5,6,7-Trimethyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-thione (**11c**). Method A*: Triazepine **11c** (0.188 g, 42%) as a mixture of two isomers in a ratio of 65:35 was prepared from of isothiocyanate **6c** (0.414 g, 2.63 mmol), NaOH (0.106 g, 2.67 mmol) and $N_2H_4 \cdot H_2O$ (0.146 g, 2.91 mmol) in H_2O (3.5 mL) (rt, 7 h) as described for compound **11b** in Method A.

Method B: Triazepine **11c** (0.962 g, 78%) as a mixture of two isomers in a ratio of 55:45 was prepared from pyrimidine **10c** (1.368 g, 7.22 mmol) and NaOH (0.290 g, 7.25 mmol) in H_2O (11 mL) (rt, 6 h) as described for compound **11b** in Method B. After crystallization from EtOH the diastereomeric ratio changed to 64:36, respectively. Mp 175.5–181 °C (EtOH). IR (Nujol) ν, cm^{-1}: 3276 (s), 3190 (br vs), 3106 (m), 1666 (m), 1568 (s), 1196 (s); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 10.14 (1H, br d, ^4J=2.2 Hz, $N_{(2)}H$), 8.52 (1H, br dd, ^3J=4.1, ^4J=2.2 Hz, $N_{(4)}H$), 3.57 (1H, ddq, ^3J=6.7, ^3J=4.1, ^3J=1.7 Hz, 5-H), 2.73 (1H, dq, ^3J=7.2, ^3J=1.7 Hz, 6-H), 1.91 (3H, s, 7-CH_3), 1.06 (3H, d, ^3J=6.7 Hz, 5-CH_3), 1.02 (3H, d, ^3J=7.2 Hz, 6-CH_3); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 10.27 (1H, br d, ^4J=2.3 Hz, $N_{(2)}H$), 8.73 (1H, br ddd, ^3J=6.2, ^4J=2.3, ^4J=1.0 Hz, $N_{(4)}H$), 3.22 (1H, ddq, ^3J=6.7, ^3J=6.2, ^3J=4.4 Hz, 5-H), 2.63 (1H, ddq, ^3J=7.1, ^3J=4.4, ^4J=1.0 Hz, 6-H), 1.95 (3H, s, 7-CH_3), 1.05 (3H, d, ^3J=6.7 Hz, 5-CH_3), 1.01 (3H, d, ^3J=7.1 Hz, 6-CH_3); ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 176.08 (C-3), 162.25 (C-7), 53.82 (C-5), 42.57 (C-6), 23.40 (7-CH_3), 18.26 (5-CH_3), 11.85 (6-CH_3); ^{13}C NMR of the minor isomer (75.48 MHz, DMSO-d_6) δ: 176.31 (C-3), 159.37 (C-7), 53.42 (C-5), 44.48 (C-6), 25.29 (7-CH_3), 21.32 (5-CH_3), 14.85 (6-CH_3); MS (EI) *m*/*z* 173 [6, $(M+2)^+$], 172 [10, $(M+1)^+$], 171 (100, M^+), 115 (32), 103 (41), 97 (22), 96 (9), 95 (16), 86 (43), 85 (86), 83 (10), 75 (12), 74 (10), 71 (12), 70 (48), 69 (36), 68 (63), 60 (36), 59 (28), 57 (16), 56 (41), 55 (38), 53 (16), 44 (32), 43 (19), 42 (39), 41 (26), 39 (13), 29 (11), 28 (17), 27 (13). Anal. Calcd for $C_7H_{13}N_3S$: C, 49.09; H, 7.65; N, 24.54. Found: C, 49.15; H, 7.80; N, 24.27.

*4.4.4. 5-Methyl-2,3,4,5,5a,6,7,8-octahydrocyclopenta[f][1,2,4]triazepine-3-thione (**11d**).* Triazepine **11d** (1.292 g, 90%) as a mixture of two isomers in a ratio of 92:8 was prepared from pyrimidine **10d** (1.573 g, 7.81 mmol) and KOH (1.100 g, 19.60 mmol) in EtOH (24 mL) (40 °C, 4 h) as described for compound **11e**. After crystallization from MeCN the diastereomeric ratio changed to 97:3, respectively. Mp 210.5 °C (dec, MeCN). IR (Nujol) ν, cm^{-1}: 3188 (br vs), 3140 (br m), 3011 (m), 1667 (m), 1573 (s), 1557 (m), 1492 (s), 1216 (s); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 10.29 (1H, br d, ^4J=2.1 Hz, $N_{(2)}H$), 8.25 (1H, br dd, ^4J=2.1, ^3J=1.5 Hz, $N_{(4)}H$), 3.33 (1H, ddq, ^3J=8.7, ^3J=6.4, ^3J=1.5 Hz, 5-H), 2.49–2.59 (1H, m, 5a-H), 2.26–2.44 (2H, m, 8-H), 1.89–2.01, 1.69–1.82, 1.47–1.63, 1.32–1.45 (1H, 1H, 1H, and 1H respectively, four m, 6-H and 7-H), 1.15 (3H, d, ^3J=6.4 Hz, CH_3); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 10.34 (1H, br d, ^4J=2.1 Hz, $N_{(2)}H$), 8.90 (1H, br dd, ^3J=6.6, ^4J=2.1 Hz, $N_{(4)}H$), 3.45 (1H, ddq, ^3J=6.6, ^3J=6.6, ^3J=3.0 Hz, 5-H), 2.88 (1H, dt, $^3J_1$+$^3J_2$=17.2, ^3J=3.0 Hz, 5a-H), 0.99 (3H, d, ^3J=6.6 Hz, CH_3), signals of other protons overlap with protons signals of the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 176.14 (C-3), 167.55 (C-8a), 54.34 (C-5), 49.20 (C-5a), 33.41 (CH_2), 29.56 (CH_2), 22.74 (CH_2), 19.82 (CH_3); MS (EI) *m*/*z* 185 [7, $(M+2)^+$], 184 [12, $(M+1)^+$], 183 (100, M^+), 168 (12), 128 (7), 115 (39), 114 (15), 112 (6), 109 (9), 97 (62), 95 (11), 86 (16), 82 (43), 81 (19), 80 (23), 79 (10), 77 (10), 70 (41), 69 (24), 67 (22), 65 (9), 60 (16), 59 (17), 55 (19), 54 (14), 53 (14), 44 (20), 42 (11), 41 (27), 39 (15), 28 (16). Anal. Calcd for $C_8H_{13}N_3S$: C, 52.43; H, 7.15; N, 22.93. Found: C, 52.43; H, 7.14; N, 22.97.

*4.4.5. 5,5-Dimethyl-2,3,4,5,5a,6,7,8-octahydrocyclopenta[f][1,2,4]triazepine-3-thione (**11e**).* To a solution of KOH (1.116 g, 19.88 mmol) in EtOH (25 mL) was added pyrimidine **10e** (1.718 g, 7.98 mmol) and the resulting mixture was stirred in a water bath (40 °C, temperature of bath) for 4 h. At the beginning of the reaction the clear solution formed and the solid material started to precipitate after 15 min. When the reaction was completed, the obtained suspension was cooled, AcOH (1.15 mL, 20.09 mmol) was added, and the solvent was removed under vacuum. To the residue was added saturated aqueous $NaHCO_3$ (5 mL), the mixture was triturated until crystallization was completed, and the obtained suspension was cooled. The precipitate was filtered, washed with ice cold H_2O, petroleum ether, and dried to give triazepine **11e** (1.439 g, 91%). Mp 254 °C (dec, MeCN) (lit.[5a] 225–228 °C). IR (Nujol) ν, cm^{-1}: 3250 (sh), 3223 (sh), 3187 (br vs), 3091 (m), 1686 (m), 1562 (s), 1196 (s); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.37 (1H, br d, ^4J=2.1 Hz, $N_{(2)}H$), 8.41 (1H, br d, ^4J=2.1 Hz, $N_{(4)}H$), 2.74 (1H, t, $^3J_1$+$^3J_2$=17.4 Hz, 5a-H), 2.29–2.38 (2H, m, 8-H), 1.89–2.03, 1.70–1.84, 1.41–1.63 (1H, 1H, and 2H, respectively, three m, 6-H and 7-H), 1.20 (3H, s, 5-CH_3), 1.05 (3H, s, 5-CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 175.16 (C-3), 165.94 (C-8a), 57.69 (C-5), 52.92 (C-5a), 34.49 (CH_2), 28.42 (CH_2), 27.46 (5-CH_3), 24.48 (5-CH_3), 23.14 (CH_2); MS (EI) *m*/*z* 199 [5, $(M+2)^+$], 198 [9, $(M+1)^+$], 197 (100, M^+), 182 (6), 164 (9), 128 (12), 123 (6), 116 (5), 115 (67), 100 (16), 97 (16), 95 (5), 94 (6), 84 (7), 83 (18), 82 (21), 81 (7), 80 (6), 79 (7), 60 (6), 59 (7), 58 (13), 55 (6), 54 (6), 53 (7), 43 (5), 42 (10), 41 (14), 39 (9), 28 (9). Anal. Calcd for $C_9H_{15}N_3S$: C, 54.79; H, 7.66; N, 21.30. Found: C, 54.70; H, 7.60; N, 21.30.

*4.4.6. 5a′,6′,7′,8′-Tetrahydro-2′H-spiro[cyclopentane-1,5′-cyclopenta[f][1,2,4]triazepine]-3′(4′H)-thione (**11f**).* Triazepine **11f** (4.125 g, 93%) was prepared from pyrimidine **10f** (4.805 g, 19.91 mmol) and KOH (2.790 g, 49.72 mmol) in EtOH (50 mL) (40 °C, 4 h) as described for compound **11e**. Mp 237–237.5 °C (dec, EtOH). IR (Nujol) ν, cm^{-1}: 3247 (br vs), 3170 (br vs), 3086 (br m), 1673 (m), 1561 (s), 1539 (m), 1216 (s); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.47 (1H, br d, ^4J=2.1 Hz, $N_{(2)}H$), 8.56 (1H, br d, ^4J=2.1 Hz, $N_{(4)}H$), 2.82 (1H, ddd, *J*=10.2, *J*=8.0, *J*=1.8 Hz, 5a-H), 2.27–2.45 (2H, m, 8-H), 1.70–2.04, 1.35–1.68 (4H, and 8H respectively, two m, 6-H, 7-H, $CH_2CH_2CH_2CH_2$); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 175.60 (C-3), 165.85 (C-8a), 67.28 (C-5), 52.54 (C-5a), 36.56 (CH_2), 34.76 (CH_2), 34.56 (CH_2), 28.79 (CH_2), 24.73 (CH_2), 23.97 (CH_2), 22.88 (CH_2); MS (EI) *m*/*z* 225 [4, $(M+2)^+$], 224 [15, $(M+1)^+$], 223 (100, M^+), 194 (5), 191 (6), 190 (44), 155 (11), 129 (9), 128 (19), 116 (5), 115 (81), 110 (8), 109 (9), 97 (12), 91 (7), 84 (10), 83 (8), 82 (20), 80 (8), 79 (12), 77 (12), 67 (25), 60 (10), 59 (6), 55 (7), 54 (7), 53 (6), 41 (12), 28 (11). Anal. Calcd for $C_{11}H_{17}N_3S$: C, 59.16; H, 7.67; N, 18.81. Found: C, 59.11; H, 7.80; N, 18.96.

*4.4.7. 5-Methyl-1,3,5a,6,7,8,9,9a-octahydro-2H-benzo[e][1,2,4]triazepine-2-thione (**11g**).* Triazepine **11g** (2.346 g, 93%) as a mixture of two isomers in a ratio of 93:7 was prepared from pyrimidine **10g** (2.765 g, 12.84 mmol) and KOH (1.801 g, 32.10 mmol) in EtOH (33 mL) (40 °C, 5 h 30 min) as described for compound **11e**. The analytically pure sample (0.163 g, a 97:3 diastereomeric mixture) was obtained from 0.408 g of crude **11g** using column chromatography on silica gel 60 (12.72 g) eluting with petroleum ether/$CHCl_3$ (from 1:1 to 1:4) followed by crystallization of the obtained solid (0.344 g) from EtOH (9 mL). Mp 210.5–211.5 °C (dec, EtOH). IR (Nujol) ν, cm^{-1}: 3215 (br vs), 3190 (br vs), 3120 (br m), 3019 (m), 1657 (m), 1580 (m), 1549 (s), 1185 (s), 1171 (s); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 10.03 (1H, br d, ^4J=2.1 Hz, $N_{(3)}H$), 7.90 (1H, br d, ^4J=2.1 Hz, $N_{(1)}H$), 3.29 (1H, ddd, ^3J=10.6, ^3J=10.2, ^3J=4.1 Hz, 9a-H), 2.68 (1H, ddd, ^3J=12.2, ^3J=10.6, ^3J=3.8 Hz, 5a-H), 1.99–2.11, 1.83–1.93, 1.51–1.69, 1.08–1.40 (1H, 1H, 2H, and 4H, respectively, four m, 6-H, 7-H, 8-H, and 9-H), 1.92 (3H, s, CH_3); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 10.17 (1H, br d, ^4J=2.2 Hz, $N_{(3)}H$), 8.26 (1H, br s, $N_{(1)}H$), 3.75–3.80 (1H, unresolved m, half-width at half-height value of 7.4 Hz, 9a-H), 1.90 (3H, s, CH_3), signals of other protons overlap with protons signals of the major

isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 177.66 (C-2), 168.05 (C-5), 60.03 (C-9a), 42.96 (C-5a), 35.01 (CH_2), 27.15 (CH_2), 23.95 (CH_2), 23.46 (CH_2), 20.06 (CH_3); MS (EI) *m*/*z* 199 [4, $(M+2)^+$], 198 [13, $(M+1)^+$], 197 (100, M^+), 182 (3), 164 (7), 140 (8), 139 (65), 137 (13), 128 (16), 127 (15), 123 (10), 122 (15), 116 (7), 115 (12), 114 (8), 110 (8), 109 (33), 107 (9), 98 (12), 97 (18), 96 (26), 95 (62), 91 (11), 85 (12), 83 (20), 82 (26), 81 (77), 79 (43), 77 (24), 72 (14), 70 (14), 69 (29), 68 (19), 67 (46), 65 (17), 60 (32), 59 (24), 57 (17), 56 (18), 55 (24), 54 (21), 53 (19), 42 (22), 41 (42), 40 (10), 39 (23), 29 (11), 28 (19), 27 (11). Anal. Calcd for $C_9H_{15}N_3S$: C, 54.79; H, 7.66; N, 21.30. Found: C, 54.83; H, 7.89; N, 21.15.

*4.4.8. 5-Methyl-2,4,5,5a,6,7,8,9-octahydro-3H-benzo[f][1,2,4]triazepine-3-thione (**11h**).* Triazepine **11h** (1.110 g, 93%) as a mixture of two isomers in a ratio of 58:42 was prepared from pyrimidine **10h** (1.307 g, 6.07 mmol) and Na (0.357 g, 15.55 mmol) in anhydrous MeOH (24 mL) (reflux, 5 h 20 min) as described for compound **11i**. The analytically pure sample (0.224 g, a 76:24 diastereomeric mixture) was obtained from 0.504 g of crude **11h** using column chromatography on silica gel 60 (9.98 g) eluting with petroleum ether/$CHCl_3$ (from 1:1 to 1:2) followed by crystallization of the obtained solid (0.472 g) from EtOH (8 mL). Mp 170–179.5 °C (dec, EtOH). IR (Nujol) ν, cm^{-1}: 3210 (br vs), 1660 (m), 1553 (s), 1202 (vs); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 10.00 (1H, br d, ^4J=2.5 Hz, $N_{(2)}H$), 8.58 (1H, br dd, ^3J=4.8, ^4J=2.5 Hz, $N_{(4)}H$), 3.34 (1H, ddq, ^3J=6.8, ^3J=6.1, ^3J=4.8 Hz, 5-H), 2.34 (1H, ddd, ^3J=11.8, ^3J=6.1, ^3J=4.3 Hz, 5a-H), 1.21–2.07 (8H, 6-H, 7-H, 8-H, and 9-H, signals overlap with signals of analogous protons of the minor isomer), 1.16 (3H, d, ^3J=6.8 Hz, CH_3); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 9.91 (1H, br d, ^4J=2.5 Hz, $N_{(2)}H$), 8.72 (1H, br dd, ^3J=4.7, ^4J=2.5 Hz, $N_{(4)}H$), 3.81 (1H, ddq, ^3J=6.9, ^3J=4.7, ^3J=2.7 Hz, 5-H), 2.49 (1H, ddd, ^3J=12.7, ^3J=4.6, ^3J=2.7 Hz, 5a-H, signals partly overlap with proton signals of the solvent), 1.21–2.07 (8H, 6-H, 7-H, 8-H, and 9-H, signals overlap with signals of analogous protons of the major isomer), 1.09 (3H, d, ^3J=6.9 Hz, CH_3); ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 182.52 (C-3), 160.90 (C-9a), 53.23 (C-5), 47.91 (C-5a), 37.03 (CH_2), 32.31 (CH_2), 27.37 (CH_2), 24.51 (CH_2), 18.92 (CH_3); ^{13}C NMR of the minor isomer (75.48 MHz, DMSO-d_6) δ: 181.18 br (C-3), 160.85 (C-9a), 51.63 (C-5), 45.99 (C-5a), 36.05 (CH_2), 27.12 (CH_2), 25.99 br (CH_2), 23.70 (CH_2), 16.77 (CH_3); MS (EI) *m*/*z* 199 [6, $(M+2)^+$], 198 [11, $(M+1)^+$], 197 (100, M^+), 182 (12), 164 (4), 154 (5), 129 (23), 115 (13), 114 (19), 113 (9), 111 (18), 101 (7), 96 (35), 95 (15), 94 (11), 91 (9), 86 (9), 84 (10), 81 (16), 79 (12), 77 (11), 70 (33), 69 (19), 67 (26), 65 (9), 60 (13), 59 (10), 55 (14), 54 (9), 53 (11), 44 (20), 42 (15), 41 (26), 39 (12), 28 (18). Anal. Calcd for $C_9H_{15}N_3S$: C, 54.79; H, 7.66; N, 21.30. Found: C, 54.81; H, 7.68; N, 21.28.

*4.4.9. 5,5-Dimethyl-2,4,5,5a,6,7,8,9-octahydro-3H-benzo[f][1,2,4]triazepine-3-thione (**11i**).* To a solution of Na (0.589 g, 25.63 mmol) in anhydrous MeOH (25 mL) was added pyrimidine **10i** (1.156 g, 5.04 mmol) and the resulting mixture was refluxed under stirring for 8 h with the protection from air moisture ($CaCl_2$-tube). The obtained solution was cooled, AcOH (1.55 mL, 27.08 mmol) was added, and the solvent was removed under vacuum. To the residue was added saturated aqueous $NaHCO_3$ (5 mL), the mixture was triturated until crystallization was completed, and the obtained suspension was cooled. The precipitate was filtered, washed with ice cold H_2O, petroleum ether, and dried to give triazepine **11i** (1.002 g, 94%). Mp 188–191 °C (EtOH). IR (Nujol) ν, cm^{-1}: 3217 (br vs), 3163 (br vs), 3125 (m), 3100 (br s), 1658 (m), 1568 (s), 1548 (m), 1483 (s), 1198 (s); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.21 (1H, br d, ^4J=2.3 Hz, $N_{(2)}H$), 8.19 (1H, br d, ^4J=2.3 Hz, $N_{(4)}H$), 2.49 (1H, dd, ^3J=11.1, ^3J=4.9 Hz, 5a-H, signals partly overlap with proton signals of the solvent), 2.13–2.34 (2H, m, 9-H), 1.68–1.91, 1.48–1.64, 1.28–1.46 (3H, 1H, and 2H, respectively, three m, 6-H, 7-H, and 8-H), 1.24 (3H, s, 5-CH_3), 1.15 (3H, s, 5-CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 177.92 (C-3), 162.96 (C-9a), 58.03 (C-5), 50.39 (C-5a), 34.70 (CH_2), 27.54 (5-CH_3), 27.03 (CH_2), 25.71 (5-CH_3), 25.10 (CH_2), 22.96 (CH_2); MS (EI) *m*/*z* 213 [3, $(M+2)^+$], 212 [10, $(M+1)^+$], 211 (73, M^+), 196 (8), 178 (7), 168 (6), 155 (8), 137 (14), 129 (79), 128 (48), 115 (79), 114 (47), 113 (15), 112 (10), 111 (41), 109 (14), 101 (14), 100 (59), 97 (16), 96 (100), 95 (49), 94 (30), 91 (15), 84 (55), 83 (59), 82 (22), 81 (33), 80 (17), 79 (35), 77 (21), 70 (9), 69 (26), 68 (15), 67 (44), 65 (13), 60 (23), 59 (19), 58 (43), 56 (9), 55 (25), 54 (14), 53 (17), 43 (12), 42 (26), 41 (51), 39 (15), 28 (12). Anal. Calcd for $C_{10}H_{17}N_3S$: C, 56.84; H, 8.11; N, 19.88. Found: C, 56.85; H, 8.13; N, 20.01.

4.5. Synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones

*4.5.1. 5,5,7-Trimethyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepin-3-one (**15a**).* A 250-mL round bottom flask equipped with magnetic stirrer, thermometer and dropping funnel was charged with a solution of KOH (13.67 g, 243.63 mmol) in H_2O (70 mL), triazepinethione **11a** (11.92 g, 69.60 mmol) and EtOH (70 mL). To the resulting stirred suspension was added H_2O_2 (28.0 mL, 415.96 mmol; *d*=1.175 g/mL, 43%) dropwise so that the internal temperature was maintained below 30 °C. Then the reaction mixture was cooled to 20 °C, stirred at room temperature for 1 h, and neutralized with concentrated aqueous HCl to pH 7 upon cooling in an ice bath. The precipitate was filtered, washed with ice cold H_2O, petroleum ether, and dried to give triazepinone **15a** (10.28 g, 95%). Mp 233–234 °C (H_2O) (lit.[5e] 214 °C). IR (Nujol) ν, cm^{-1}: 3235 (br s), 3167 (m), 3098 (br s), 3024 (m), 1682 (s), 1651 (s); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.81 (1H, br d, ^4J=2.1 Hz, $N_{(2)}H$), 6.63 (1H, unresolved br d, $N_{(4)}H$), 2.45 (2H, d, ^4J=0.8 Hz, H-6), 1.95 (3H, s, 7-CH_3), 1.16 (6H, s, 5-CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 157.41, 155.17 (C-3, C-7), 53.56 (C-5), 43.94 (C-6), 30.23 (5-CH_3), 25.49 (7-CH_3); MS (EI) *m*/*z* 156 [1, $(M+1)^+$], 155 (6, M^+), 140 (1), 100 (12), 99 (100), 97 (33), 84 (45), 72 (41), 70 (7), 67 (5), 58 (11), 57 (13), 56 (32), 53 (5), 43 (5), 42 (19), 41 (18), 39 (10), 29 (5), 28 (6).

*4.5.2. 5a′,6′,7′,8′-Tetrahydro-2′H-spiro[cyclopentane-1,5′-cyclopenta[f][1,2,4]triazepine]-3′(4′H)-one (**15b**).* To a stirred solution of KOH (0.816 g, 14.55 mmol) in H_2O (3 mL) were added triazepinethione **11f** (0.646 g, 2.89 mmol) and EtOH (11 mL). To the resulting suspension was added H_2O_2 (1.95 mL, 28.97 mmol; *d*=1.175 g/mL, 43%) over 1 min. After 10–15 min the reaction mixture began to warm, starting material gradually dissolved and new precipitate formed. (*Note*: With increased charges the *internal* temperature of reaction mixture should be maintained below 55 °C). The obtained suspension was stirred at room temperature for 1.5 h, AcOH (0.7 mL, 12.23 mmol) was added, and the solvent was removed under vacuum (temperature of bath below 35 °C). To the residue was added saturated aqueous $NaHCO_3$ (3 mL), and the obtained suspension was cooled. The precipitate was filtered, washed with ice cold H_2O, petroleum ether, and dried to give triazepinone **15b** (0.539 g, 90%). Mp 233.5–234.5 °C (dec, EtOH). IR (Nujol) ν, cm^{-1}: 3281 (br s), 3205 (br s), 3125 (s), 3079 (br s), 1691 (s), 1655 (s); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.18 (1H, br d, ^4J=2.4 Hz, $N_{(2)}H$), 7.06 (1H, br d, ^4J=2.4 Hz, $N_{(4)}H$), 2.69 (1H, ddd, *J*=10.9, *J*=8.1, *J*=1.8 Hz, 5a-H), 2.24–2.38 (2H, m, 8-H), 1.92–2.03, 1.33–1.85 (1H, and 11H, respectively, two m, 6-H, 7-H, $CH_2CH_2CH_2CH_2$); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 158.31, 155.44 (C-3, C-8a), 62.06 (C-5), 51.76 (C-5a), 36.95 (CH_2), 34.52 ($2CH_2$), 28.84 (CH_2), 24.28 (CH_2), 23.78 (CH_2), 22.40 (CH_2); MS (EI) *m*/*z* 208 [37, $(M+1)^+$], 207 (100, M^+), 190 (25), 178 (8), 135 (12), 122 (9), 121 (11), 112 (28), 109 (21), 108 (12), 107 (11), 100 (15), 99 (88), 97 (12), 94 (12), 93 (12), 91 (22), 84 (61), 82 (18), 81 (16), 80 (18), 79 (23), 78 (11), 77 (19), 68 (12), 67 (60), 65 (21), 55 (20), 54 (37), 53 (23), 42 (15), 41 (46), 39 (20), 28 (14). Anal.

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Calcd for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.75; H, 8.24; N, 20.32.

*4.5.3. 5-Methyl-1,3,5a,6,7,8,9,9a-octahydro-2H-benzo[e][1,2,4]triazepin-2-one (**15c**).* To a stirred solution of KOH (0.885 g, 15.78 mmol) in H_2O (5 mL) were added triazepinethione **11g** (1.038 g, 5.26 mmol; a 93:7 diastereomeric mixture) and EtOH (15 mL) and the resulting suspension was cooled in an ice bath. Then H_2O_2 (2.2 mL, 32.68 mmol; d=1.175 g/mL, 43%) was added over 9 min. During the addition the solid material dissolved and almost at the same time the new precipitate formed. The ice bath was removed after 5 min from the completion of the addition. (*Note*: With increased charges the *internal* temperature of reaction mixture should be maintained below 20 °C). The obtained suspension was stirred at room temperature for 1 h, AcOH (0.80 mL, 13.97 mmol) was added, solid $NaHCO_3$ was added until pH of the reaction mixture was 8. The solvent was removed under vacuum, the wet residue was co-evaporated with toluene (2×15 mL), and then the flask with the residue was dried in a vacuum desiccator (over P_2O_5) to constant weight. The obtained material was purified using column chromatography on silica gel 60 (18.41 g) eluting with MeOH/$CHCl_3$ (from 1:100 to 1:50). The main fraction was concentrated, the residual foam was triturated with ether until crystallization was complete, the resulting suspension was cooled (−18 °C). The precipitate was filtered, washed with cold (−18 °C) ether (3×2 mL), and dried to give triazepinone **15c** (0.563 g, 59%) as a mixture of two isomers in a ratio of 95:5. (*Note*: compound **15c** is water soluble, isolation of product as described for other triazepinones afforded **15c** in 39% yield). Crystallization from EtOH gave triazepinone **15c** as a single diastereomer. Mp 226–227 °C (EtOH). IR (Nujol) ν, cm^{-1}: 3225 (br vs), 3089 (br vs), 1685 (vs), 1632 (m); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.64 (1H, br d, ^4J=2.1 Hz, $N_{(3)}H$), 6.38 (1H, br d, ^4J=2.1 Hz, $N_{(1)}H$), 3.11 (1H, ddd, ^3J=11.0, ^3J=10.3, ^3J=4.1 Hz, 9a-H), 2.58 (1H, ddd, ^3J=12.1, ^3J=11.0, ^3J=3.6 Hz, 5a-H), 1.89 (3H, s, CH_3), 1.82–1.97, 1.55–1.69, 1.09–1.39 (2H, 2H, and 4H respectively, three m, 6-H, 7-H, 8-H, and 9-H); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 8.85 (1H, br d, ^4J=2.5 Hz, $N_{(3)}H$), 6.80 (1H, br s, $N_{(1)}H$), 3.63–3.68 (1H, unresolved m, half-width at half-height value of 7.4 Hz, 9a-H), 1.83 (3H, s, CH_3), signals of other protons overlap with protons signals of the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 163.73, 156.60 (C-2, C-5), 56.32 (C-9a), 43.36 (C-5a), 35.32 (CH_2), 27.34 (CH_2), 24.30 (CH_2), 23.61 (CH_2), 20.05 (CH_3); MS (EI) m/z 182 [5, $(M+1)^+$], 181 (46, M^+), 166 (1), 153 (11), 140 (13), 139 (14), 138 (10), 137 (13), 123 (15), 112 (11), 111 (9), 110 (20), 109 (47), 100 (10), 99 (24), 97 (43), 96 (55), 95 (100), 93 (9), 91 (14), 86 (10), 85 (96), 83 (40), 82 (49), 81 (50), 80 (25), 79 (52), 77 (24), 72 (20), 70 (21), 69 (50), 68 (36), 67 (74), 65 (19), 57 (40), 56 (56), 55 (50), 54 (42), 53 (37), 44 (13), 43 (17), 42 (34), 41 (54), 39 (25), 29 (14), 28 (20), 27 (13). Anal. Calcd for $C_9H_{15}N_3O$: C, 59.65; H, 8.34; N, 23.19. Found: C, 59.63; H, 8.21; N, 23.16.

*4.5.4. 5,5-Dimethyl-2,4,5,5a,6,7,8,9-octahydro-3H-benzo[f][1,2,4]triazepin-3-one (**15d**).* To a stirred solution of KOH (0.599 g, 10.67 mmol) in H_2O (3 mL) were added triazepinethione **11i** (0.751 g, 3.55 mmol) and EtOH (11 mL) and the resulting suspension was cooled in an ice bath. Then H_2O_2 (1.5 mL, 21.54 mmol; d=1.163 g/mL, 42%) was added over 12 min. After addition was completed the solid material started to dissolve and almost at the same time the new precipitate formed. The change of solid materials should be monitored (in this experiment it took about 20 min), and *only after* completion of this process the ice bath was removed. (*Note*: With increased charges the *internal* temperature of reaction mixture should be maintained below 20 °C). The obtained suspension was stirred at room temperature for 1.5 h, AcOH (0.402 mL, 7.02 mmol) was added, and the solvent was removed under vacuum (temperature of bath below 35 °C). To the residue was added saturated aqueous $NaHCO_3$, and the obtained suspension was cooled. The precipitate was filtered, washed with ice cold H_2O, petroleum ether, and dried to give triazepinone **15d** (0.582 g, 84%). Mp 195–196 °C (EtOH). IR (Nujol) ν, cm^{-1}: 3253 (br vs), 3120 (br s), 1689 (vs), 1645 (s); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.93 (1H, br d, ^4J=2.5 Hz, N_2H), 6.61 (1H, br d, ^4J=2.5 Hz, N_4H), 2.22–2.35, 2.07–2.18, 1.71–1.88, 1.22–1.55 (2H, 1H, 3H, and 3H, respectively, four m, 5a-H, 6-H, 7-H, 8-H, and 9-H), 1.22 (3H, s, 5-CH_3), 1.10 (3H, s, 5-CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 157.39 br, 157.21 (C-3, C-9a), 52.34 (C-5), 51.05 (C-5a), 36.46 (CH_2), 28.49 (5-CH_3), 27.81 (CH_2), 26.53 (CH_2), 25.96 (5-CH_3), 24.13 (CH_2); MS (EI) m/z 196 [5, $(M+1)^+$], 195 (37, M^+), 180 (6), 166 (2), 152 (12), 139 (9), 138 (11), 137 (16), 127 (7), 126 (6), 113 (24), 112 (63), 111 (58), 109 (10), 99 (95), 96 (14), 95 (25), 94 (14), 93 (9), 91 (10), 84 (45), 82 (14), 81 (29), 80 (12), 79 (26), 77 (18), 69 (15), 68 (10), 67 (32), 65 (11), 58 (100), 55 (19), 54 (11), 53 (17), 43 (8), 42 (18), 41 (24), 39 (9), 28 (9). Anal. Calcd for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.51; H, 8.69; N, 21.49.

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Supplementary data

Supplementary data (procedures for directed aldol type condensations, copies of IR, ^{1}H and ^{13}C NMR spectra of synthesized compounds, 2D NMR spectra of compounds **11a**–**c**, computational details) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.03.082. These data include MOL files and InChiKeys of the most important compounds described in this article.

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