

Proceedings



# A General Stereoselective Approach to 1,2,4-Triazepane-3-thiones/ones via Reduction or Reductive Alkylation of 2,4,5,6-Tetrahydro-3*H*-1,2,4triazepine-3-thiones/ones <sup>+</sup>

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- + Presented at the 22nd International Electronic Conference on Synthetic Organic Chemistry, 15 November– 15 December 2018; Available Online: https://sciforum.net/conference/ecsoc-22.

Published: 14 November 2018

**Abstract:** A general stereoselective approach to previously unknown 1,2,4-triazepane-3-thiones/ones based on reduction or reductive alkylation of readily available 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones/ones has been developed. The approach involved treatment of tetrahydrotriazepines with sodium cyanoborohydride in MeOH at pH 3 or with sodium borohydride and excess of carboxylic acid in tetrahydrofuran to give 1-unsubstituted or 1-alkyl-substituted 1,2,4-triazepane-3-thiones/ones, respectively. The latter were also prepared by reaction of 1-unsubstituted 1,2,4-triazepane-3-thiones/ones with sodium cyanoborohydride and aldehyde in MeOH in the presence of AcOH.

**Keywords:** 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones/ones; 1,2,4-triazepane-3-thiones/ones; reduction; reductive alkylation

## 1. Introduction

Development of efficient approaches to rare heterocyclic scaffolds is a fundamental challenge of organic synthesis and medicinal chemistry. 1,2,4-Triazepines, particularly 1,2,4-triazepin-3-ones/ thiones are representatives of these scaffolds [1–6]. They are of great interest because of their diverse pharmacological properties. For example, 1,2,4-triazepin-3-ones/thiones are effective antagonists of parathyroid hormone 1 (PTH1R) [7] and holecystokinin hormone 2 (CCK<sub>2</sub>) [8,9] receptors. Some of them possess antioxidant [10], antipsychotic [11,12], and HIV protease inhibitory activities [13–15].

The reported syntheses of 1,2,4-triazepin-3-ones/thiones include the reaction of  $\beta$ -isocyanato and  $\beta$ -isothiocyanato ketones with hydrazines [16–24], condensation of semicarbazides and thiosemicarbazides with various 1,3-dicarbonyl compounds or their derivatives [10,25–33], reaction of arylidene ketones with N<sub>2</sub>H<sub>4</sub>·2HNCS [34], addition of semicarbazides and thiosemicarbazides to  $\alpha$ , $\beta$ -unsaturated carbonyl compounds or their synthetic equivalents [35–39], reaction of  $\gamma$ -hydrazinosubstituted amines with phosgene equivalents [8,13–15,40], and intramolecular cyclization of 4-( $\gamma$ oxoalkyl)semicarbazides and 4-( $\gamma$ -oxoalkyl)thiosemicarbazides or their derivatives [17,22,41,42]. Generally, these methods give access to 1,2,4-triazepin-2- ones/thiones with one or two double bonds in the 7-membered ring. Their saturated representatives, particularly 1,2,4-triazepan-3-ones/ thiones 1 (Figure 1) remain practically inaccessible since the methods designed to produce these compounds mostly result in smaller-sized rings. For example, the condensation of 2-substituted thiosemicarbazides with 2,2-disubstituted malonyl chlorides was reported to give 5,7-dioxo-1,2,4triazepane-3-thiones [43,44]. However, reinvestigation of this reaction showed that in most cases the only products formed were azetidine-2,4-diones [32], with the exception of the reaction between 2-phenylthiosemicarbazide and 2,2-diethyl malonyl chloride affording the corresponding azetidine-2,4-dione (59%) along with 6,6-diethyl-5,7-dioxo-2-phenyl-1,2,4-triazepane-3-thione (2%).



Figure 1. General formula of 1,2,4-triazepane-3-thiones/ones 1 and structure of nonpeptidic HIV protease inhibitor 2.

The only relevant approach to triazepanes is based on the reaction of poorly available chiral nonracemic  $\gamma$ -hydrazino-substituted amines with phosgene equivalents to give the derivatives of 6hydroxy-1,2,4-triazepan-3-ones. It should be noted that these compounds are the key precursors for preparation of potent nonpeptidic HIV protease inhibitors (e.g., **2**) [13–15].

Syntheses of triazepane-3-thiones/ones without functional groups at the 5, 6, and 7 positions, cyclic thiosemicarbazides, and semicarbazides, have not been reported. Thus, the development of reliable and practical approaches to non-functionalized triazepane-3-thiones/ones is of great interest from the viewpoint of synthetic, theoretical, and medicinal chemistry. We rationalized that these compounds could be prepared by reductive transformations of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-2-ones/thiones. Previously, we developed effective syntheses of the latter based on acid-catalyzed cyclization of 4-(3-aryl-3-oxopropyl)(thio)semicarbazides and their hydrazones [18,42] or base-promoted ring expansion of 3-amino-4-hydroxyhexahydropyrimidine-2-thiones [19].

Here, we describe general stereoselective syntheses of previously unknown 1-unsubstituted or 1-alkyl substituted 1,2,4-triazepane-3-thiones/ones via reduction or reductive alkylation of tetrahydro-3*H*-1,2,4-triazepine-3-thiones/ones.

#### 2. Results and Discussion

Readily available 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones/ones **3a–k** [18,19,42] served as starting material for the present investigation. Among a large variety of reductants which could be used for C=N double bond reduction [45–50] we chose sodium cyanoborohydride [51–55]. We have found that triazepines **3a–k** smoothly reacted with NaBH<sub>3</sub>CN (1.00–1.61 equiv.) in MeOH under slightly acidic conditions (pH about 3) at room temperature to give the corresponding 1-unsubstituted triazepanes **4a–k** in high yields (Scheme 1, Table 1). The pH was maintained by the addition of 2N HCl in MeOH with methyl orange as an internal indicator.



Scheme 1. Synthesis of 1-unsubstituted 1,2,4-triazepane-3-thiones/ones 4a-k.

The reduction rate strongly depended on the structure of triazepines 3a-k and generally increased in the case of triazepin-3-ones compared with triazepine-3-thiones (Table 1; entry 5 vs. entry 6; entry 8 vs. entry 9; entry 10 vs. entry 11), 5-monosubstituted triazepines compared with 5,5-

disubstituted ones (entry 3 vs. entries 4, 5, and 6; entry 7 vs. entry 8), and monocyclic triazepines compared with bicyclic ones (entries 1 and 2 vs. entries 4, 5, 6, and 8).

Entry	3	x	R	R <sup>1</sup>	R <sup>2</sup>	<b>R</b> <sup>3</sup>	Equiv. of NaBH3CN	Time (h)	Product	Isolated Yield (%)	<i>cis/trans</i> Ratio <sup>b</sup>
1	3a	S	Me	Me	Н	Me	1.00	1	1 <b>4a</b> 93		_
2	3b	0	Me	Me	Н	Me	1.00	1	4b	54	-
3	<b>3c</b> <sup><i>c</i></sup>	S	Me	Н	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>		1.01	1	4c	94	d
4	3d	S	Me	Me	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>		1.48	3.17	4 <b>d</b>	88	>99:1
5	3e	S	CH <sub>2</sub> C	H <sub>2</sub> CH <sub>2</sub>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>		1.61	3.17	4e	92	>99:1
6	3f	0	CH <sub>2</sub> C	H <sub>2</sub> CH <sub>2</sub>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>		1.49	1	<b>4f</b>	91	99:1
7	3g <sup>e</sup>	S	Me	Н	CH <sub>2</sub> CH	2CH2CH2	1.00	1	<b>4</b> g	84	f
8	3h	S	Me	Me	CH <sub>2</sub> CH	2CH2CH2	1.50	1	4h	93	98:2
9	3i	0	Me	Me	CH <sub>2</sub> CH	2CH2CH2	1.01	1	<b>4i</b>	94	88:12
10	3j	S	Ph	Н	Н	Ph	1.51	3	4j	99	26:74
11	3k	0	Ph	Н	Н	Ph	1.00	1	<b>4</b> k	93	18:82

**Table 1.** Synthesis of 1-unsubstituted 1,2,4-triazepane-3-thiones/ones **4a–k** by reduction of **3a–k** with NaBH<sub>3</sub>CN in MeOH at room temperature (pH 3)<sup>*a*</sup>.

<sup>*a*</sup> Level of conversion of the starting material is 100%. <sup>*b*</sup> According to <sup>1</sup>H NMR spectroscopic data for the crude product. <sup>*c*</sup> A 92:8 mixture of (5*R*\*,5*aR*\*)- and (5*S*\*,5*aR*\*)-diastereomers (ref. [19]). <sup>*d*</sup> A nearly pure (5*R*\*,6*R*\*,7*R*\*)-diastereomer (>96%). <sup>*e*</sup> A 60:40 mixture of (5*R*\*,5*aR*\*)- and (5*S*\*,5*aR*\*)- and (5*S*\*,5*aR*\*)-diastereomers (ref. [19]). <sup>*f*</sup> A mixture of (5*R*\*,6*R*\*,7*R*\*)- and (5*R*\*,6*R*\*,7*S*\*)-diastereomers in a ratio of 60:40, respectively.

Reduction of the C=N bond in **3a–k** results in formation of a new stereocenter at the C7 atom. Diastereoselectivity of this reaction varies from good to excellent (Table 1). Due to strong 1,2-asymmetric induction bicyclic triazepines **3d–f**,**h** gave practically single ( $6R^*,7S^*$ )-diastereomers of triazepanes **4d–f**,**h** with *cis*-relationship between two rings (*cis/trans*  $\ge$  98:2) (entries 4–6, and 8). With triazepine **3i** the reaction diastereoselectivity slightly decreased, and a mixture of *cis-* and *trans*-isomers of **4i** was obtained in a ratio of 88:12 (entry 9). Reduction of diphenyl-substituted monocyclic triazepines **3j**,**k** showed further decrease in selectivity to result in mixtures of *cis-* and *trans*-diastereomers of triazepanes **4j**,**k** in a ratio of 74:26 and 82:18, respectively (entries 10 and 11).

Next, we studied reduction of bicyclic 5-methyl triazepines **3c** and **3g** possessing two stereocenters which were obtained as mixtures of two diastereomers in a ratio of 92:8 and 60:40, respectively [19]. We have found that practically single ( $5R^*$ , $6R^*$ , $7R^*$ )-diastereomer (>96%) of **4c** formed in 94% yield from **3c** (entry 3) and a 60:40 mixture of ( $5R^*$ , $6R^*$ , $7R^*$ )- and ( $5R^*$ , $6S^*$ , $7S^*$ )-diastereomers of **4g** formed in 84% yield from **3g** (entry 7). With both triazepines **3c** and **3g** strong 1,2-asymmetric induction led exclusively to triazepanes **4c**,**g** with *cis*-relationship between two rings. Based on these data, the relative configuration of the major and minor isomers of starting compounds **3c**,**g** could be unambiguously assigned as ( $5R^*$ , $5aR^*$ ) and ( $5S^*$ , $5aR^*$ ), respectively [19].

We suppose that the first step of the reduction of triazepines **3a–k** under the described conditions is protonation of either the oxo/thioxo-group or the imino nitrogen affording hydrochlorides **5a–k** or **6a–k**, respectively (Scheme 2).

The density functional theory calculations performed at the B3LYP/6-311++G(d,p) level of theory for cations **5d**,**h**,**i**,**k** and **6d**,**h**,**i**,**k** with pseudo-axial and pseudo-equatorial orientation of the 5-Ph group (for **5k** and **6k**) or C6-CH<sub>2</sub> bond (for **5d**,**h**,**i** and **6d**,**h**,**i**) using the polarizable continuum model showed that the *N*-protonated cations **6d**,**h**,**i**,**k** are significantly more stable than the corresponding *O*- or *S*-protonated cations **5d**,**h**,**i**,**k** (1.8–8.1 kcal/mol in MeOH). Therefore, formation of **5a–k** can be excluded. The final step of the reaction is hydride transfer from NaBH<sub>3</sub>CN to the initially generated hydrochlorides **6a–k** to give the target products **4a–k**.



Scheme 2. A plausible pathway for the reduction of 3a-k into 4a-k.

High diastereoselectivity in the reduction of 3c-k can be explained in terms of steric approach control. The equatorial attack of the reducing reagent to the imine carbon of intermediate cations 6c-k is preferable. The axial attack is complicated by van der Waals repulsions with two axial cyclohexane hydrogens in 6g-i, two pseudo-axial cyclopentane hydrogens in 6c-f or pseudo-axial 5-H hydrogen in 6j,k. This conclusion is confirmed by the DFT B3LYP/6-311++G(d,p) optimized geometries (in MeOH) of the most stable conformers of cations 6d,h,i,k with pseudo-axial and pseudo-equatorial position of the 5-Ph group (for 6k) or C6-CH<sub>2</sub> bond (for 6d,h,i). Three representative examples with favored (a) and unfavored (b) attack of BH<sub>3</sub>CN-anion to the equatorial conformers of cations 6d,i,k are shown in Figure 2.



**Figure 2.** Favored (**a**) and unfavored (**b**) approach of BH<sub>3</sub>CN-anion to *N*-protonated triazepines: **6i** (**i**), **6d** (**ii**), and **6k** (**iii**).

Crude triazepanes **4a–k** were purified by crystallization (for **4a,d–f,h–j**) or using silica gel column chromatography followed by crystallization (for **4b,c,g,k**). It should be noted that after purification triazepanes **4c–f,h,j,k** were obtained as practically single diastereomers ( $dr \ge 95\%$ ).

The structure of compounds **4a-k** was established by spectroscopic data. The <sup>1</sup>H NMR spectra of **4a–k** in DMSO-*d*<sub>6</sub> show a long-range coupling between the (thio)amide N(2)H and N(4)H protons ( $^{4}J = 2.0-2.5$  Hz) that indicates their one-plane W-shaped arrangement. Similar long-range couplings are characteristic of *N*-unsubstituted (thio)ureide-containing heterocycles, e.g., 2,3,4,5-tetrahydro- and 2,3-dihydro-1*H*-1,3-diazepin-2-ones [56–60], hexahydro- and 1,2,3,4-tetrahydropyrimidine-2-thiones/ones [56–67], 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones/ones [18,19,42]. Signal of the N(1)H proton in **4a–k** appears as a doublet of doublets at 4.23–6.36 ppm with vicinal couplings <sup>3</sup>*J*<sub>N(1)H,N(2)H</sub> = 0–3.5 and <sup>3</sup>*J*<sub>N(1)H,H-7</sub> = 4.2–11.1 Hz. The relative configurations of the stereogenic centers in **4c,d,f,i–k** and the minor isomers of **4g,h** were assigned based on the analysis of couplings between protons of the triazepane ring. For example, high values of vicinal couplings between the H-5 and H-6 protons (10.5 Hz) and between the H-7 and N(1)H protons (10.8 Hz) in **4c** indicate that these protons

are antiperiplanar, and therefore, this compound has  $(5R^*,6R^*,7R^*)$ -configuration. The *cis*-relationship between the cyclopentane and triazepane rings in **4c** is also confirmed by a relatively high value of vicinal coupling between the H-6 and H-7 protons (8.2 Hz). High values of vicinal couplings  ${}^{3}J_{H-5,H-6} = 10.5$  Hz and  ${}^{3}J_{H-6,H-7} = 10.8$  Hz observed in the  ${}^{1}$ H NMR spectrum of the minor diastereomer of **4j** prove that two phenyl groups have *cis*-arrangement. The major diastereomer of **4j** has *trans*-configuration with a pseudo-axial orientation of the 5-Ph group ( ${}^{3}J_{N(4)H,H-5} = 5.2$ ,  ${}^{3}J_{H-5,H-6} = 2.5$  Hz) and a pseudo-equatorial orientation of the 7-Ph group ( ${}^{3}J_{H-6,H-7} = 9.2$  Hz).

Two alternative procedures were developed for preparation of 1-alkyl-substituted 1,2,4triazepane-3-thiones/ones. The first involves reductive alkylation of 2,4,5,6-tetrahydro-3*H*-1,2,4triazepine-3-thiones/ones **3** with sodium borohydride in carboxylic acid media [68–71]. We found that monocyclic triazepines **3a**,**b** smoothly reacted with NaBH<sub>4</sub> (6 equiv.) in the presence of AcOH or EtCOOH (60.3–61.9 equiv.) in THF at room temperature for 23.5–24 h to give the corresponding 1ethyl- or 1-propyltriazepanes **7a**,**b**,**e**,**f** in 50–90% yields (Scheme 3; Table 2, entries 1, 2, 6, and 7).



Scheme 3. Synthesis of 1-alkyl-substituted 1,2,4-triazepane-3-thiones/ones 7a–n by the reductive alkylation.

Under similar conditions (THF, rt, 24 h), the reaction of diphenyl triazepine **3k** with NaBH<sub>4</sub> (5.9 equiv.) in the presence of AcOH (63.4 equiv.) gave a mixture of starting material **3k** and 1-ethyltriazepane **7n** in a ratio of 21:79, respectively. This reaction was completed with 10 equivalents of NaBH<sub>4</sub> and 108.3 equivalents of AcOH to produce the target **7n** in 94% yield with excellent *trans*-diastereoselectivity (*trans:cis* = 98:2, Table 2, entry 16). Higher stereoselectivity in the reduction of **3k** with NaBH(OAc)<sub>3</sub>, in situ generated from NaBH<sub>4</sub> and AcOH [68], compared with NaBH<sub>3</sub>CN (*trans:cis* = 82:18, Table 1, entry 11) can be explained in terms of steric approach control (see Figure 2) considering a greater steric bulk of reducing reagent in the first case.

Cyclohexane-fused triazepine **3g** [a 60:40 mixture of  $(5R^*,5aR^*)$ - and  $(5S^*,5aR^*)$ -isomers] reacted with NaBH<sub>4</sub> (6.1 equiv.) in the presence of AcOH (65.4 equiv.) or EtCOOH (62.2 equiv.) in THF (rt, 24 h) with very high stereoselectivity to give mixtures  $(5R^*,6R^*,7R^*)$ - and  $(5S^*,6R^*,7R^*)$ -diastereomers (*cis*-relationship between two rings) of triazepanes **7k**,**1** in a ratio of 61:39 and 58:42, respectively (entries 13 and 14). Reduction of cyclopentane-fused triazepine **3c** also proceeded with very high stereoselectivity but the reaction rate relatively decreased. Under optimized conditions, the reaction between this compound [a 92:8 mixture of  $(5R^*,5aR^*)$ - and  $(5S^*,5aR^*)$ -isomers] and NaBH<sub>4</sub> (10 equiv.) in the presence of AcOH (104 equiv.) (THF, rt, 24 h) afforded a 91:9 mixture of  $(5R^*,6R^*,7R^*)$ - and  $(5S^*,6R^*,7R^*)$ -diastereomers of **7g** with *cis*-fused rings (entry 8).

The alternative approach to 1-alkyl-substituted 1,2,4-triazepane-3-thiones/ones 7 involves reductive alkylation of their 1-unsubstituted analogs 4 under the action of aldehyde and NaBH<sub>3</sub>CN in the presence of AcOH (Scheme 3). Treatment of 4a,c,e,h with aliphatic aldehydes (5.8–6.4 equiv.), NaBH<sub>3</sub>CN (1.5–1.6 equiv.) and AcOH (1.5 equiv.) in MeOH at room temperature for 2 h resulted in the corresponding triazepanes 7b,c,g,h,j,m in high yields (Table 2, entries 3, 4, 9, 10, 12, and 15). Under the same conditions, compounds 4a,e were reacted with benzaldehyde (6.1 equiv.), NaBH<sub>3</sub>CN (3.1–3.6 equiv.) and AcOH (3.0–3.1 equiv.) to give triazepanes 7d,i in 90 and 93% yields, respectively (entries 5 and 11).

Entry	3 or 4	x	R	$\mathbb{R}^1$	R <sup>2</sup>	<b>R</b> <sup>3</sup>	R <sup>4</sup>	Reaction conditions <sup>b</sup>		Yield (%) <sup>c</sup>	dr <sup>d</sup>
1	3a	S	Me	Me	Н	Me	Me	NaBH4 (6.0), AcOH (61.1), THF, rt, 24 h	7a	89	-
2	3a	S	Me	Me	Н	Me	Et	NaBH4 (6.0), EtCOOH (61.9), THF, rt, 24 h	7b	90	_
3	4a	S	Me	Me	Н	Me	Et	NaBH3CN (1.5), EtCHO (5.8), AcOH (1.5), MeOH, rt, 2 h	7b	90	-
4	4a	S	Me	Me	Н	Me	Pr	NaBH3CN (1.5), PrCHO (6.0), AcOH (1.5), MeOH, rt, 2 h	7c	95	-
5	4a	S	Me	Me	Н	Me	Ph	NaBH3CN (3.6), PhCHO (6.1), AcOH (3.0), MeOH, rt, 2 h	7d	90	-
6	3b	0	Me	Me	Н	Me	Me	NaBH4 (6.0), AcOH (60.3), THF, rt, 24 h	7e	50	_
7	3b	0	Me	Me	Н	Me	Et	NaBH4 (6.0), EtCOOH (60.6), THF, rt, 23.5 h	7f	50	-
8	3c <sup>e</sup>	S	Me H		CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>		Me	NaBH4 (10.1), AcOH (104.1), THF, rt, 24 h	7g	31	_ <i>f</i>
9	4c	S	Me H		CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>		Me	NaBH3CN (1.6), MeCHO (6.4), AcOH (1.5), MeOH, rt, 2 h	7g	87	>99:1
10	4e	S	CH2CH2CH2		CH2CH2CH2		Et	NaBH3CN (1.5), EtCHO (6.1), AcOH (1.5), MeOH, rt, 2 h	7h	95	>99:1
11	4e	S	CH2CH2CH2		CH2CH2CH2		Ph	NaBH3CN (3.1), PhCHO (6.1), AcOH (3.1), MeOH, rt, 2 h	7i	93	>99:1
12	<b>4f</b> <i>s</i>	0	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>		CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>		Et	NaBH3CN (1.5), EtCHO Et (6.2), AcOH (1.5), MeOH, rt, 2 h		68	99:1
13	$3g^{h}$	S	Me	Н	CH₂CH	2CH2CH2	Me	NaBH4 (6.1), AcOH (65.4), THF, rt, 24 h	7k	85	_ i
14	<b>3g</b> <sup><i>h</i></sup>	S	Me	Н	CH <sub>2</sub> CH	2CH2CH2	Et	NaBH4 (6.1), EtCOOH (62.2), THF, rt, 24 h	71	68	_ j
15	<b>4h</b> <sup><i>k</i></sup>	S	Me Me CH2C		CH <sub>2</sub> CH	CH2CH2CH2 Et		NaBH3CN (1.5), EtCHO (6.0), AcOH (1.5), MeOH, rt, 2 h	7m	96	>99:1
16	3k	0	Ph	Н	Н	Ph	Me	NaBH4 (10.1), AcOH (208.4), THF, rt, 24 h	7n	94	2:98

**Table 2.** Synthesis of 1-substituted 1,2,4-triazepane-3-thiones/ones **7a–n** by the reductive alkylation of **3a–c,g,k** and **4a,c,e,f,h**<sup>*a*</sup>.

<sup>*a*</sup> Level of conversion of the starting material is 100%. <sup>*b*</sup> Number in parentheses is the number of equivalents. <sup>*c*</sup> Isolated yield. <sup>*d*</sup> dr—*cis/trans*-diastereomeric ratio according to <sup>1</sup>H NMR spectroscopic data for the crude product. <sup>*e*</sup> A 92:8 mixture of  $(5R^*,5aR^*)$ - and  $(5S^*,5aR^*)$ -diastereomers (ref. [19]). <sup>*f*</sup> A 91:9 mixture of  $(5R^*,6R^*,7R^*)$ - and  $(5S^*,6R^*,7R^*)$ -diastereomers. <sup>*s*</sup> A 99:1 mixture of  $(6R^*,7S^*)$ - and  $(6R^*,7R^*)$ -diastereomers. <sup>*k*</sup> A 60:40 mixture of  $(5R^*,6R^*,7R^*)$ -diastereomers. <sup>*j*</sup> A 58:42 mixture of  $(5R^*,6R^*,7R^*)$ - and  $(5S^*,6R^*,7R^*)$ -diastereomers. <sup>*k*</sup> A 98:2 mixture of  $(6R^*,7S^*)$ - and  $(6R^*,7R^*)$ -diastereomers. <sup>*k*</sup> A 98:2 mixture of  $(6R^*,7S^*)$ - and  $(6R^*,7R^*)$ -diastereomers. <sup>*k*</sup> A 98:2 mixture of  $(6R^*,7S^*)$ - and  $(6R^*,7R^*)$ -diastereomers.

Generally, the two-step approach to 1-alkyl-substituted 1,2,4-triazepane-3-thiones/ones ( $3 \rightarrow 4 \rightarrow 7$ ) was more effective. For instance, following this method compound 7g was obtained from 3c in 82% overall yield, while direct reductive alkylation of 3c with the NaBH<sub>4</sub>/AcOH system gave 7g only in 31% yield.

The structures of compounds 7a-n were confirmed by spectroscopic data. The relative configurations of the stereogenic centers in 7g-n were assigned by analysis of proton coupling constants in the triazepane ring as described above for compounds 4.

### 3. Conclusions

A convenient stereoselective synthesis of *N*-unsubstituted 1,2,4-triazepane-3-thiones/ones based on the reduction of readily available 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones/ones with sodium cyanoborohydride in MeOH at pH 3 has been developed. Stereochemistry of the reduction was explained in terms of steric control approach of BH<sub>3</sub>CN-anion to N1-protonated substrate. The obtained 1,2,4-triazepane-3-thiones/ones were converted into 1-alkyl-substituted derivatives by reductive alkylation with sodium cyanoborohydride and aldehyde in MeOH in the presence of AcOH. Alternatively, 1-alkyl-1,2,4-triazepane-3-thiones/ones were prepared with high stereoselectivity by treatment of tetrahydrotriazepines with sodium borohydride and excess of carboxylic acid in THF.

Acknowledgements: This research was financially supported by the Russian Foundation for Basic Research (Grant No. 19-316-70006).

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