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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*-1,2,4-triazepine-3-thiones/ones †

Anastasia A. Fesenko and Anatoly D. Shutalev *

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky Ave., 119991 Moscow, Russian Federation

* Correspondence: anatshu@gmail.com, shad@ioc.ac.ru

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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 THF 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]. 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) [2] and holecystokinin hormone 2 (CCK_2) [3] receptors. Some of them possess antioxidant [4], antipsychotic [5], and HIV protease inhibitory activities [6].

The reported syntheses of 1,2,4-triazepin-3-ones/thiones include the reaction of β-isocyanato and β-isothiocyanato ketones with hydrazines [7, 8], condensation of semicarbazides and thiosemicarbazides with various 1,3-dicarbonyl compounds or their derivatives [4, 9], reaction of arylidene ketones with $N_2H_4 \cdot 2HNCS$ [10], addition of semicarbazides and thiosemicarbazides to α,β-unsaturated carbonyl compounds or their synthetic equivalents [11], reaction of γ-hydrazino-substituted amines with phosgene equivalents [3a, 6, 12], and intramolecular cyclization of 4-(γ-oxoalkyl)semicarbazides and 4-(γ-oxoalkyl)thiosemicarbazides or their derivatives [7b, 8e, 13]. 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-1,2,4-triazepane-3-thiones [14]. However, reinvestigation of this reaction showed that in most cases the only products formed were azetidine-2,4-diones [9h], 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%).

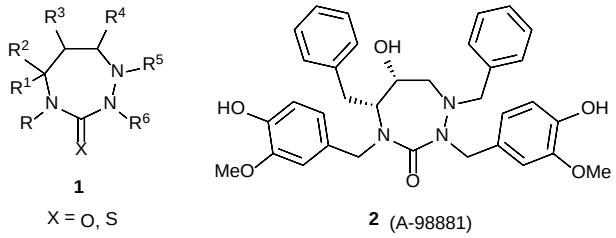


Figure 1. General formula of 1,2,4-triazepane-3-thiones/ones **1** and structureof nonpeptidic HIV protease inhibitor **2**.

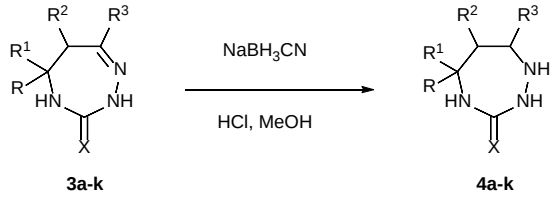
The only relevant approach to triazepanes is based on the reaction of poorly available chiral non-racemic γ-hydrazino-substituted amines with phosgene equivalents to give the derivatives of 6-hydroxy-1,2,4-triazepan-3-ones. It should be noted that these compounds are the key precursors for preparation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

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 [8a, 13b] or base-promoted ring expansion of 3-amino-4-hydroxyhexahydropyrimidine-2-thiones [8b].

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** [8a,b, 13b] served as starting material for the present investigation. Among a large variety of reductants which could be used for C=N double bond reduction [15] we chose sodium cyanoborohydride [16]. We have found that triazepines **3a-k** smoothly reacted with $NaBH_3CN$ (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 [17].



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).

Table 1. Synthesis of 1-unsubstituted 1,2,4-triazepane-3-thiones/ones **4a-k** by reduction of **3a-k** with $NaBH_3CN$ in MeOH at room temperature (pH 3).[a]

Entry	3	X	R	R^1	R^2	R^3	Equiv. of $NaBH_3CN$	Time (h)	Product	Isolated yield (%)	*cis*/*trans* ratio[b]
1	**3a**	S	Me	Me	H	Me	1.00	1	**4a**	93	–
2	**3b**	O	Me	Me	H	Me	1.00	1	**4b**	54	–
3	**3c**[c]	S	Me	H	$CH_2CH_2CH_2$		1.01	1	**4c**	94	–[d]
4	**3d**	S	Me	Me	$CH_2CH_2CH_2$		1.48	3.17	**4d**	88	>99:1
5	**3e**	S	$CH_2CH_2CH_2$		$CH_2CH_2CH_2$		1.61	3.17	**4e**	92	>99:1
6	**3f**	O	$CH_2CH_2CH_2$		$CH_2CH_2CH_2$		1.49	1	**4f**	91	99:1
7	**3g**[e]	S	Me	H	$CH_2CH_2CH_2CH_2$		1.00	1	**4g**	84	–[f]
8	**3h**	S	Me	Me	$CH_2CH_2CH_2CH_2$		1.50	1	**4h**	93	98:2
9	**3i**	O	Me	Me	$CH_2CH_2CH_2CH_2$		1.01	1	**4i**	94	88:12
10	**3j**	S	Ph	H	H	Ph	1.51	3	**4j**	99	26:74
11	**3k**	O	Ph	H	H	Ph	1.00	1	**4k**	93	18:82

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

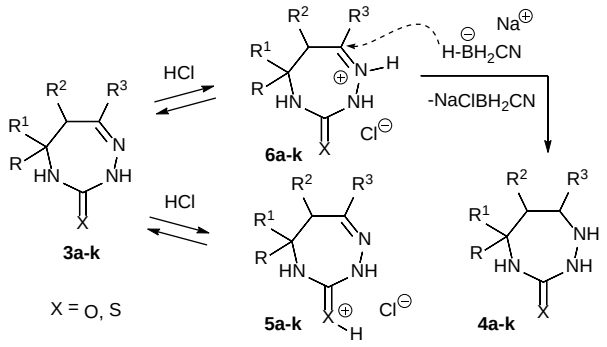
Reduction of the C=N bond in **3a-k** results in formation of a new stereocenter at the C7 atom. Diastereoselectivity of this reaction varies from good to excellent (Table 1). Due to strong 1,2-asymmetric induction bicyclic triazepines **3d-f**,**h** gave practically single (6*R**,7*S**)-diastereomers of triazepanes **4d-f,h** with *cis*-relationship between two rings (*cis*/*trans* ≥ 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 [8b]. We have found that practically single (5*R**,6*R**,7*R**)-diastereomer (> 96%) of **4c** formed in 94% yield from **3c** (entry 3) and a 60:40 mixture of (5*R**,6*R**,7*R**)- and (5*R**,6*S**,7*S**)-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 (5*R**,5a*R**) and (5*S**,5a*R**), respectively [8b].

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 DFT 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_2 bond (for **5d,h,i** and **6d,h,i**) using the PCM 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 $NaBH_3CN$ 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_2 bond (for **6d,h,i**). Three representative examples with favored (**a**) and unfavored (**b**) attack of BH_3CN-anion to the equatorial conformers of cations **6d,i,k** are shown in Figure 2.

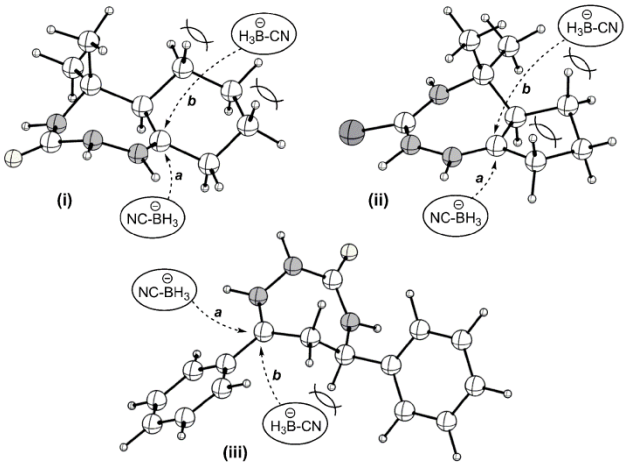


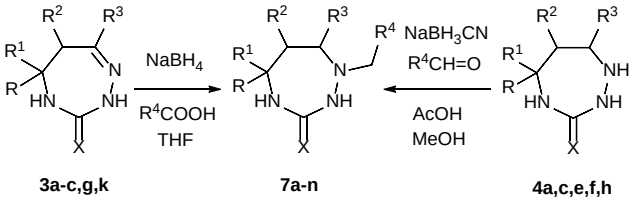
Figure 2. Favored (**a**) and unfavored (**b**) approach of BH_3CN-anion to *N*-protonated triazepines: **6i** (i), **6d** (ii), and **6k** (iii).

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* ≥95%).

The structure of compounds **4a-k** was established by spectroscopic data. The ^1H NMR spectra of **4a-k** in DMSO-d_6 show a long-range coupling between the (thio)amide N(2)H and N(4)H protons (^4J = 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 [18], hexahydro- and 1,2,3,4-tetrahydropyrimidine-2-thiones/ones [18, 19], 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones/ones [8a,b, 13b]. 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

$^3J_{N(1)H,N(2)H}$ = 0–3.5 and $^3J_{N(1)H,H-7}$ = 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 (5*R**,6*R**,7*R**)-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 $^3J_{H-5,H-6}$ = 10.5 Hz and $^3J_{H-6,H-7}$ = 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 ($^3J_{N(4)H,H-5}$ = 5.2, $^3J_{H-5,H-6}$ = 2.5 Hz) and a pseudo equatorial orientation of the 7-Ph group ($^3J_{H-6,H-7}$ = 9.2 Hz).

Two alternative procedures were developed for preparation of 1-alkyl-substituted 1,2,4-triazepane-3-thiones/ones. The first involves reductive alkylation of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones/ones **3** with sodium borohydride in carboxylic acid media [20]. We found that monocyclic triazepines **3a,b** smoothly reacted with $NaBH_4$ (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 1-ethyl- 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 $NaBH_4$ (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 $NaBH_4$ 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 $NaBH(OAc)_3$, in situ generated from $NaBH_4$ and AcOH [20a], compared with $NaBH_3CN$ (*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 (5*R**,5a*R**)- and (5*S**,5a*R**)-isomers] reacted with $NaBH_4$ (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 (5*R**,6*R**,7*R**)- and (5*S**,6*R**,7*R**)-diastereomers (*cis*-relationship between two rings) of triazepanes **7k,l** 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 (5*R**,5a*R**)- and (5*S**,5a*R**)-isomers] and $NaBH_4$ (10 equiv.) in the presence of AcOH (104 equiv.) (THF, rt, 24 h) afforded a 91:9 mixture of (5*R*,6R*,7R*)*- and (5*S*,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 $NaBH_3CN$ in the presence of AcOH (Scheme 3). Treatment of **4a,c,e,h** with aliphatic aldehydes (5.8–6.4 equiv.), $NaBH_3CN$ (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.), $NaBH_3CN$ (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).

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**.[a]

Entry	**3** or **4**	X	R	R^1	R^2	R^3	R^4	Reaction conditions[b]	**7**	Yield (%)[c]	dr[d]
1	**3a**	S	Me	Me	H	Me	Me	$NaBH_4$ (6.0), AcOH (61.1), THF, rt, 24 h	**7a**	89	–
2	**3a**	S	Me	Me	H	Me	Et	$NaBH_4$ (6.0), EtCOOH (61.9), THF, rt, 24 h	**7b**	90	–
3	**4a**	S	Me	Me	H	Me	Et	$NaBH_3CN$ (1.5), EtCHO (5.8), AcOH (1.5), MeOH, rt, 2 h	**7b**	90	–
4	**4a**	S	Me	Me	H	Me	Pr	$NaBH_3CN$ (1.5), PrCHO (6.0), AcOH (1.5), MeOH, rt, 2 h	**7c**	95	–
5	**4a**	S	Me	Me	H	Me	Ph	$NaBH_3CN$ (3.6), PhCHO (6.1), AcOH (3.0), MeOH, rt, 2 h	**7d**	90	–
6	**3b**	O	Me	Me	H	Me	Me	$NaBH_4$ (6.0), AcOH (60.3), THF, rt, 24 h	**7e**	50	–
7	**3b**	O	Me	Me	H	Me	Et	$NaBH_4$ (6.0), EtCOOH (60.6), THF, rt, 23.5 h	**7f**	50	–
8	**3c**[e]	S	Me	H	$CH_2CH_2CH_2$		Me	$NaBH_4$ (10.1), AcOH (104.1), THF, rt, 24 h	**7g**	31	–[f]
9	**4c**	S	Me	H	$CH_2CH_2CH_2$		Me	$NaBH_3CN$ (1.6), MeCHO (6.4), AcOH (1.5), MeOH, rt, 2 h	**7g**	87	>99:1
10	**4e**	S	$CH_2CH_2CH_2$		$CH_2CH_2CH_2$		Et	$NaBH_3CN$ (1.5), EtCHO (6.1), AcOH (1.5), MeOH, rt, 2 h	**7h**	95	>99:1
11	**4e**	S	$CH_2CH_2CH_2$		$CH_2CH_2CH_2$		Ph	$NaBH_3CN$ (3.1), PhCHO (6.1), AcOH (3.1), MeOH, rt, 2 h	**7i**	93	>99:1
12	**4f**[g]	O	$CH_2CH_2CH_2$		$CH_2CH_2CH_2$		Et	$NaBH_3CN$ (1.5), EtCHO (6.2), AcOH (1.5), MeOH, rt, 2 h	**7j**	68	99:1
13	**3g**[h]	S	Me	H	$CH_2CH_2CH_2CH_2$		Me	$NaBH_4$ (6.1), AcOH (65.4), THF, rt, 24 h	**7k**	85	–[i]
14	**3g**[h]	S	Me	H	$CH_2CH_2CH_2CH_2$		Et	$NaBH_4$ (6.1), EtCOOH (62.2), THF, rt, 24 h	**7l**	68	–[j]
15	**4h**[k]	S	Me	Me	$CH_2CH_2CH_2CH_2$		Et	$NaBH_3CN$ (1.5), EtCHO (6.0), AcOH (1.5), MeOH, rt, 2 h	**7m**	96	>99:1
16	**3k**	O	Ph	H	H	Ph	Me	$NaBH_4$ (10.1), AcOH (208.4), THF, rt, 24 h	**7n**	94	2:98

[a] Level of conversion of the starting material is 100%.
[b] Number in parentheses is the amount of equivalents.
[c] Isolated yield.
[d] dr – *cis*/*trans* diastereomeric ratio according to ^{1}H NMR spectroscopic data for the crude product.
[e] A 92:8 mixture of (5*R**,5a*R**)- and (5*S**,5a*R**)-diastereomers (ref. 8b).
[f] A 91:9 mixture of (5*R**,6*R**,7*R**)- and (5*S**,6*R**,7*R**)-diastereomers.
[g] A 99:1 mixture of (6*R**,7*S**)- and (6*R**,7*R**)-diastereomers.
[h] A 60:40 mixture of (5*R**,5a*R**)- and (5*S**,5a*R**)-diastereomers (ref. 8b).
[i] A 61:39 mixture of (5*R**,6*R**,7*R**)- and (5*S**,6*R**,7*R**)-diastereomers.
[j] A 58:42 mixture of (5*R**,6*R**,7*R**)- and (5*S**,6*R**,7*R**)-diastereomers.
[k] A 98:2 mixture of (6*R**,7*S**)- and (6*R**,7*R**)-diastereomers.

Generally, the two-step approach to 1-alkyl-substituted 1,2,4-triazepane-3-thiones/ones (**3** → **4** → **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 $NaBH_4$/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_3CN-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.

References

1. For reviews on 1,2,4-triazepines, see: (*a*) J. T. Sharp, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, Vol. 7, pp 593–651; (*b*) T. Tsuchiya, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Elsevier, Oxford, 1996, Vol. 9, pp 309–331; (*c*) G. I. Yranzo and E. L. Moyano, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Amsterdam, 2008, Vol. 13, pp 399–430; (*d*) N. P. Peet, in *The Chemistry of Heterocyclic Compounds*, ed. A. Rosowsky, John Wiley, New York, 1984, Vol. 43, Part 2, pp 719–842; (*e*) G. Léna and G. Guichard, *Curr. Org. Chem.,* 2008, **12**, 813–835; (*f*) K. M. Elattar, M. A. Abozeid, I. A. Mousa and A. El-Mekabaty, *RSC Advances,* 2015, **5**, 106710–106753.
2. I. M. McDonald, C. Austin, I. M. Buck, D. J. Dunstone, J. Gaffen, E. Griffin, E. A. Harper, R. A. D. Hull, S. B. Kalindjian, I. D. Linney, C. M. R. Low, D. Patel, M. J. Pether, M. Raynor, S. P. Roberts, M. E. Shaxted, J. Spencer, K. I. M. Steel, D. A. Sykes, P. T. Wright and W. Xun, *J. Med. Chem.,* 2007, **50**, 4789–4792.
3. (*a*) I. M. McDonald, C. Austin, I. M. Buck, D. J. Dunstone, E. Griffin, E. A. Harper, R. A. D. Hull, S. B. Kalindjian, I. D. Linney, C. M. R. Low, M. J. Pether, J. Spencer, P. T. Wright, T. Adatia and A. Bashall, *J. Med. Chem.,* 2006, **49**, 2253–2261; (*b*) K. Kaur and T. T. Talele, *J. Mol. Graphics Modell.,* 2008, **27**, 409–420.
4. M. Sankaran, C. Kumarasamy, U. Chokkalingam and P. S. Mohan, *Bioorg. Med. Chem. Lett.,* 2010, **20**, 7147–7151.
5. (*a*) S. M. Ibrahim, M. Abo-Kul, M. K. Soltan, W. Barakat and A. S. Helal, *Med. Chem.,* 2014, **4**, 351–356; (*b*) S. M. Ibrahim, M. M. Baraka, O. I. El-Sabbagh, H. Kothayer, *Med. Chem. Res.,* 2013, **22**, 1488–1496.
6. (*a*) C. Zhao, H. L. Sham, M. Sun, V. S. Stoll, K. D. Stewart, S. Lin, H. Mo, S. Vasavanonda, A. Saldivar, C. Park, E. J. McDonald, K. C. Marsh, L. L. Klein, D. J. Kempf and D. W. Norbeck, *Bioorg. Med. Chem. Lett.,* 2005, **15**, 5499–5503; (*b*) H. L. Sham, C. Zhao, K. D. Stewart, D. A. Betebenner, S. Lin, C. H. Park, X.-P. Kong, W. Rosenbrook, T. Herrin, D. Madigan, S. Vasavanonda, N. Lyons, A. Molla, A. Saldivar, K. C. Marsh, E. McDonald, N. E. Wideburg, J. F. Denissen, T. Robins, D. J. Kempf, J. J. Plattner and D. W. Norbeck, *J. Med. Chem.,* 1996, **39**, 392–397; (*c*) C. N. Hodge, C. H. Fernandez, P. K. Jadhav and P. Y. Lam, WO 9422840, 1994; *Chem. Abs.*, 1994, **123**, 33104.
7. (*a*) R. Lantzsch and D. Arlt, *Synthesis,* 1977, 756–757; (*b*) W. A. Mosher and R. B. Toothill, *J. Heterocycl. Chem.,* 1971, **8**, 209–214.
8. (*a*) A. A. Fesenko, M. S. Grigoriev and A. D. Shutalev, *Tetrahedron,* 2016, **72**, 7952–7967; (*b*) A. A. Fesenko and A. D. Shutalev, *Tetrahedron,* 2016, **72**, 2560–2573; (*c*) N. A. Danilkina, L. E. Mikhaylov and B. A. Ivin, *Chem. Heterocycl. Compd.,* 2011, **47**, 886–900; (*d*) B. Rezessy, Z. Zubovics, J. Kovács and G. Tóth, *Tetrahedron,* 1999, **55**, 5909–5922; (*e*) P. Richter and K. Steiner, in *Studies in Organic Chemistry*, ed. H. C. van der Plas, L. Ötvös and M. Simonyi, Elsevier, Amsterdam, 1984, Vol. 18 (Bio-Organic Heterocycles), pp 217–220; (*f*) R. Neidlein and W. D. Ober, *Monatsh. Chem.*, 1976, **107**, 1251–1258; (*g*) G. Zigeuner, A. Fuchsgruber and F. Wede, *Monatsh. Chem.*, 1975, **106**, 1495–1497.
9. (*a*) M. M. Hassan, E. S. Othman and M. Abass, *Res. Chem. Intermed.*, 2013, **39**, 1209–122; (*b*) A. Chaudhary, S. C. Joshi and R. V. Singh, *Main Group Met. Chem.*, 2004, **27**, 59–70; (*c*) S. S. Ibrahim, Z. M. El-Gendy, H. A. Allimony and E. S. Othman, *Chem. Papers,* 1999, **53**, 53–64; (*d*) A. Hasnaoui, J.–P. Lavergne and P.

Viallefont, *Recl. Trav. Chim. Pays-Bas,* 1980, **99**, 301–306; (*e*) A. Hasnaoui, J.–P. Lavergne and P. Viallefont, *J. Heterocycl. Chem.,* 1978, **15**, 71–75; (*f*) B. Stanovnik and M. Tišler, *Naturwissenschaften,* 1965, **52**, 207; (*g*) G. Losse and W. Farr, *J. Prakt. Chem.,* 1959, **8**, 298–305; (*h*) A. Ebnöther, E. Jucker, E. Rissi, J. Rutschmann, E. Schreier, R. Steiner, R. Süess and A. Vogel, *Helv. Chim. Acta,* 1959, **42**, 918–955; (*i*) G. Losse, W. Hessler, A. Barth, *Chem. Ber.,* 1958, **91**, 150–157.

10. W. Seebacher, G. Michl and R. Weis, *Tetrahedron Lett.,* 2002, **43**, 7481–7483.
11. (*a*) A. A. Hassan, T. M. Bebair, M. El-Gamal, *J. Chem. Res.,* 2014, 27–31; (*b*) A. A. Aly, A. A. Hassan, E. M. El-Sheref, M. A. Mohamed and A. B. Brown, *J. Heterocycl. Chem.,* 2008, **45**, 521–526; (*c*) A. A. El-Helby, M. A. Amin, M. M. El-Sawah, A. H. Bayoni, A. S. El-Azab, F. F. Sherbiny, *J. Saudi Chem. Soc.,* 2006, **10**, 77–93; (*d*) H. Abdel-Ghany, A. Khodairy, H. M. Moustafa, *Synth. Commun.,* 2000, **30**, 1257–1268; (*e*) M. Kobayashi, J. Tanaka, T. Katori, M. Marsuura, M. Yamashita and I. Kitagawa, *Chem. Pharm. Bull.,* 1990, **38**, 2409–2418.
12. R. S. Hosmane, V. S. Bhadti and B. B. Lim, *Synthesis,* 1990, 1095–1100.
13. (*a*) L. A. Trafimova, M. O. Zimin and A. D. Shutalev, *J. Chem. Res.,* 2017, **41**, 149–156; (*b*) A. A. Fesenko and A. D. Shutalev, *Tetrahedron,* 2015, **71**, 9528–9543.
14. (*a*) G. Losse and H. Uhlig, *Chem. Ber.,* 1957, **90**, 257–260; (*b*) G. Losse, E. Wottgen and H. Just, *J. Prakt. Chem.,* 1958, **7**, 28–37.
15. For selected reviews, see: (*a*) R. O. Hutchins and M. K. Hutchins, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, Vol. 8, pp 25–78; (*b*) R. Hemmer and W. Lürken, in *Houben-Weyl Methods of Organic Chemistry*, Thieme, Stuttgart, 1992, Vol. E 16d, pp 646–1234; (*c*) *Modern Reduction Methods*, ed. P. G. Andersson and I. J. Munslow, Wiley-VCH Verlag, Weinheim, 2008; (*d*) T. C. Nugenta and M. El-Shazly, *Adv. Synth. Catal.,* 2010, **352**, 753– 819; (*e*) R. W. Layer, *Chem. Rev.,* 1963, **63**, 489–510; (*f*) R. P. Tripathi, S. S. Verma, J. Pandey and V. K. Tiwar, *Curr. Org. Chem.,* 2008, **12**, 1093–1115.
16. (*a*) R. O. Hutchins, M. K. Hutchins and M. L. Crawley, in *e-EROS: Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, 2007, doi:10.1002/047084289X.rs059.pub2; (*b*) J. Seyden-Penne, *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd ed.; Wiley-VCH, New York, 1997; (*c*) C. F. Lane, *Synthesis,* 1975, 135–146; (*d*) R. O. Hutchins and N. R. Natale, *Org. Prep. Proced. Int.,* 1979, **11**, 201–246; (*e*) R. F. Borch, M. D. Bernstein and H. D. Durst, *J. Am. Chem. Soc.,* 1971, **93**, 2897–2904.
17. Using compound **3a** as an example, we demonstrated that, in the absence of HCl, the reduction with $NaBH_3CN$ (1.5 equiv) in MeOH proceeded neither at room temperature (1.5 h) nor under reflux (1 h).
18. (*a*) A. A. Fesenko, M. S. Grigoriev and A. D. Shutalev, *J. Org. Chem.,* 2017, **82**, 8085−8110; (*b*) A. A. Fesenko and A. D. Shutalev, *Tetrahedron Lett.,* 2014, **55**, 1416−1420; (*c*) A. A. Fesenko, A. A. Trafimova and A. D. Shutalev, *Org. Biomol. Chem.,* 2012, **10**, 447−462; (*d*) A. A. Fesenko and A. D. Shutalev, *Tetrahedron,* 2011, **67**, 6876−6882; (*e*) A. A. Fesenko, M. L. Tullberg and A. D. Shutalev, *Tetrahedron,* 2009, **65**, 2344−2350.
19. (*a*) P. A. Solovyev, A. A. Fesenko and A. D. Shutalev, *J. Fluor. Chem.,* 2016, **182**, 28–33; (*b*) A. A. Fesenko and A. D. Shutalev, *Tetrahedron,* 2014, **70**, 5398–5414; (*c*) A. A. Fesenko and A. D. Shutalev, *J. Org. Chem.,* 2013, **78**, 1190−1207; (*d*) A. A. Fesenko, E. A. Dem'yachenko, G. A. Fedorova and A. D. Shutalev, *Monatsh. Chem.,* 2013, **144**, 351−359; (*e*) A. A. Fesenko, P. A. Solovyev and A. D. Shutalev, *Tetrahedron,* 2010, **66**, 940−946; (*f*) A. A. Fesenko and A. D. Shutalev, *Tetrahedron Lett.,* 2007, **48**, 8420−8423; (*g*) A. D. Shutalev and N. N. Kurochkin, *Mendeleev Commun.,* 2005, **15**, 70−72.
20. For reviews on this reductive system, see: (*a*) G. W. Gribble and C. F. Nutaitis, *Org. Prep. Proced. Int.,* 1985, **17**, 317−384; (*b*) A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff and R. D. Shah, *J. Org. Chem.,* 1996, **61**, 3849–3862; (*c*) E. W. Baxter and A. B. Reitz, *Org. React.,* 2002, **59**, 1–714; (*d*) A. F. Abdel-Magid and S. J. Mehrman, *Org. Proc. Res. Dev.,* 2006, **10**, 971–1031.