proceedings

MDPI

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*-1,2,4-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, Russia; af240182@yandex.ru

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

† 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_2) [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 β-isocyanato and β-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 $N_2H_4{\cdot}2HNCS$ [34], addition of semicarbazides and thiosemicarbazides to α,β-unsaturated carbonyl compounds or their synthetic equivalents [35–39], reaction of γ-hydrazino-substituted amines with phosgene equivalents [8,13–15,40], and intramolecular cyclization of 4-(γ-oxoalkyl)semicarbazides and 4-(γ-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-1,2,4-

triazepane-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%).

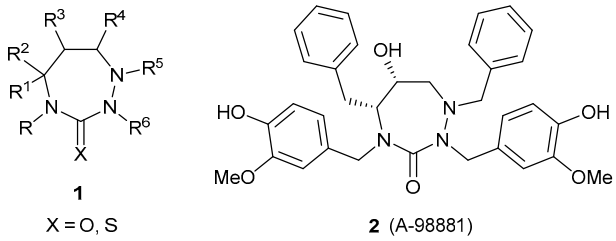


Figure 1. General formula of 1,2,4-triazepane-3-thiones/ones **1** and structure of nonpeptidic HIV protease inhibitor **2**.

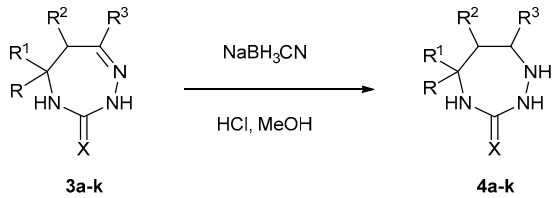
The only relevant approach to triazepanes is based on the reaction of poorly available chiral non-racemic γ-hydrazino-substituted amines with phosgene equivalents to give the derivatives of 6-hydroxy-1,2,4-triazepan-3-ones. It should be noted that these compounds are the key precursors for preparation of potent nonpeptidic HIV protease inhibitors (e.g., **2**) [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 $NaBH_3CN$ (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 [56].



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

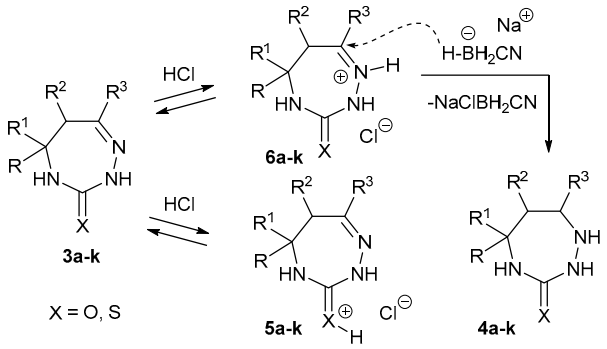
[a] Level of conversion of the starting material is 100%. [b] According to ^1H NMR spectroscopic data for the crude product. [c] A 92:8 mixture of (5*R**,5a*R**)- and (5*S**,5a*R**)-diastereomers (ref. [19]). [d] A nearly pure (5*R**,6*R**,7*R**)-diastereomer (>96%). [e] A 60:40 mixture of (5*R**,5a*R**)- and (5*S**,5a*R**)-diastereomers (ref. [19]). [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 [19]. 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 [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_2 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 $NaBH_3CN$ 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.

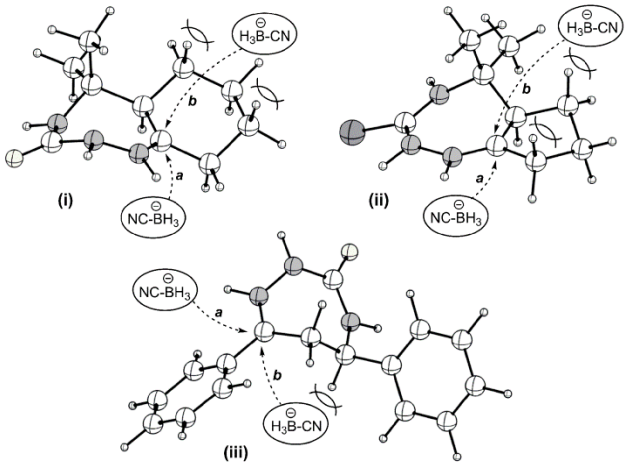


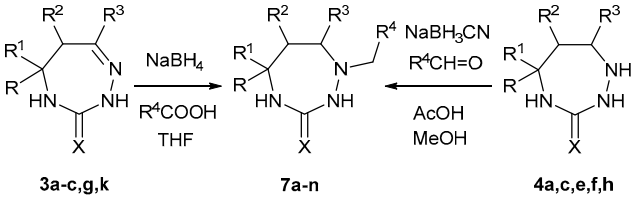
Figure 2. Favored (**a**) and unfavored (**b**) approach of BH_3CN-anion to *N*-protonated triazepines: **6i** (**i**), **6d** (**ii**), and **6k** (**iii**).

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 ^{1}H 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 [57–61], hexahydro- and 1,2,3,4-tetrahydropyrimidine-2-thiones/ones [57–68], 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 $^3J_{N(1)H,N(2)H}$ = 0–3.5 and $^3J_{N(1)H,H\text{-}7}$ = 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 $^{3}J_{H\text{-}5,H\text{-}6}$ = 10.5 Hz and $^{3}J_{H\text{-}6,H\text{-}7}$ = 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 ($^{3}J_{N(4)H,H\text{-}5}$ = 5.2, $^{3}J_{H\text{-}5,H\text{-}6}$ = 2.5 Hz) and a pseudo-equatorial orientation of the 7-Ph group ($^{3}J_{H\text{-}6,H\text{-}7}$ = 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 [69–72]. 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 [69], 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**,6*R**,7*R**)- and (5*S**,6*R**,7*R**)-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 number 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. [19]). [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. [19]). [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.

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

References

1. Sharp, J.T. Seven-membered Rings with Two or More Heteroatoms. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A.R., Rees, C.W., Eds.; Pergamon: Oxford, UK, 1984; Volume 7, pp. 593–651.
2. Tsuchiya, T. Seven-membered Rings with Three Heteroatoms 1,2,4. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A.R., Rees, C.W., Scriven, E.F.V., Eds.; Elsevier: Oxford, UK, 1996; Volume 9, pp. 309–331.
3. Yranzo, G.I.; Moyano, E.L. Seven-membered Rings with Three Heteroatoms 1,2,4. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A.R., Ramsden, C.A., Scriven, E.F.V., Taylor, R.J.K., Eds.; Elsevier: Amsterdam, The Netherlands, 2008; Volume 13, pp. 399–430.
4. Peet, N.P. Monocyclic and Condensed Triazepines and Tetrazepines. In *The Chemistry of Heterocyclic Compounds*; Rosowsky, A., Ed.; John Wiley: New York, NY, USA, 1984; Volume 43, Part 2, pp. 719–842.
5. Léna, G.; Guichard, G. Synthetic Methods for the Preparation of Triazepandiones and Review of their Applications. *Curr. Org. Chem.* **2008**, *12*, 813–835.
6. Elattar, K.M.; Abozeid, M.A.; Mousa, I.A.; El-Mekabaty, A. Advances in 1,2,4-triazepines chemistry. *RSC Adv.* **2015**, *5*, 106710–106753.
7. McDonald, I.M.; Austin, C.; Buck, I.M.; Dunstone, D.J.; Gaffen, J.; Griffin, E.; Harper, E.A.; Hull, R.A.D.; Kalindjian, S.B.; Linney, I.D.; et al. Discovery and Characterization of Novel, Potent, Non-Peptide Parathyroid Hormone-1 Receptor Antagonists. *J. Med. Chem.* **2007**, *50*, 4789–4792.
8. McDonald, I.M.; Austin, C.; Buck, I.M.; Dunstone, D.J.; Griffin, E.; Harper, E.A.; Hull, R.A.D.; Kalindjian, S.B.; Linney, I.D.; Low, C.M.R.; et al. Novel, Achiral 1,3,4-Benzotriazepine Analogues of 1,4-Benzodiazepine-Based CCK_2 Antagonists That Display High Selectivity over CCK_1 Receptors. *J. Med. Chem.* **2006**, *49*, 2253–2261.
9. Kaur, K.; Talele, T.T. 3D QSAR studies of 1,3,4-benzotriazepine derivatives as CCK_2 receptor antagonists. *J. Mol. Graph. Model.* **2008**, *27*, 409–420.
10. Sankaran, M.; Kumarasamy, C.; Chokkalingam, U.; Mohan, P.S. Synthesis, antioxidant and toxicological study of novel pyrimido quinoline derivatives from 4-hydroxy-3-acyl quinolin-2-one. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7147–7151.
11. Ibrahim, S.M.; Abo-Kul, M.; Soltan, M.K.; Barakat, W.; Helal, A.S. Synthesis and Biological Screening of New Derivatives of 2,3-dihydro quinazolin-4(1H)-one and Benzotriazepin- 5(2H)-one for Central Nervous System Activity. *Med. Chem*. **2014**, *4*, 351–356.
12. Ibrahim, S.M.; Baraka, M.M.; El-Sabbagh, O.I.; Kothayer, H. Synthesis of new benzotriazepin-5(2*H*)-one derivatives of expected antipsychotic activity. *Med. Chem. Res.* **2013**, *22*, 1488–1496.
13. Zhao, C.; Sham, H.L.; Sun, M.; Stoll, V.S.; Stewart, K.D.; Lin, S.; Mo, H.; Vasavanonda, S.; Saldivar, A.; Park, C.; et al. Synthesis and activity of *N*-acyl azacyclic urea HIV-1 protease inhibitors with high potency against multiple drug resistant viral strains. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5499–5503.
14. Sham, H.L.; Zhao, C.; Stewart, K.D.; Betebenner, D.A.; Lin, S.; Park, C.H.; Kong, X.-P.; Rosenbrook, W.; Herrin, T.; Madigan, D.; et al. A Novel, Picomolar Inhibitor of Human Immunodeficiency Virus Type 1 Protease. *J. Med. Chem.* **1996**, *39*, 392–397.
15. Hodge, C.N.; Fernandez, C.H.; Jadhav, P.K.; Lam, P.Y. Preparation of substituted caprolactams and derivatives useful for treatment of HIV disease. WO 9422840, 1994; *Chem. Abstr.* **1994**, *123*, 33104.
16. Lantzsch, R.; Arlt, D. Herstellung und Reaktionen von 1,1-Dimethyl-3-oxobutyl-isocyanat. *Synthesis* **1977**, *11*, 756–757.
17. Mosher, W.A.; Toothill, R.B. Investigation of Routes to Indeno[2,1-*f*]-2*H*-1,2,4-triazepinediones. *J. Heterocycl. Chem.* **1971**, *8*, 209–214.
18. Fesenko, A.A.; Grigoriev, M.S.; Shutalev, A.D. Synthesis of aryl substituted 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones/ones starting from chalcone-derived β-isothiocyanato ketones. *Tetrahedron*, **2016**, *72*, 7952–7967.

19. Fesenko, A.A.; Shutalev, A.D. Base-promoted ring expansion of 3-aminopyrimidine-2-thiones into 1,2,4-triazepine-3-thiones. *Tetrahedron* **2016**, *72*, 2560–2573.
20. Danilkina, N.A.; Mikhaylov, L.E.; Ivin, B.A. Reaction of Acetylenedicarboxylic Acids Esters with 4,5-Dihydro-1*H*-pyrazole-1-carbothioamides and 3,4,5,6-Tetrahydro-2*H*-1,2,4-triazepine-3-thiones. *Chem. Heterocycl. Compd.* **2011**, *47*, 886–900.
21. Rezessy, B.; Zubovics, Z.; Kovács, J.; Tóth, G. Synthesis and structure elucidation of new thiazolotriazepines. *Tetrahedron* **1999**, *55*, 5909–5922.
22. Richter, P.; Steiner, K. Chalcone as Starting Material for Synthesis of 1,2,4-Triazepines. In *Studies in Organic Chemistry*; van der Plas, H.C., Ötvös, L., Simonyi, M., Eds.; Elsevier: Amsterdam, The Netherlands, 1984; Volume 18, pp. 217–220.
23. Neidlein, R.; Ober, W.D. Synthesen von Siebenerringsystemen aus substituierten Isothiocyanaten und Hydrazinen. *Monatsh. Chem.* **1976**, *107*, 1251–1258.
24. Zigeuner, G.; Fuchsgruber, A.; Wede, F. Notiz zur Struktur des Umsetzungsproduktes von 4-Isothiocyanato-4-methyl-2-pentanon mit Hydrazin—Uber das 2,4,5,6-Tetrahydro-5,5,7-trimethyl- 3*H*-1,2,4-triazepin-3-thion. *Monatsh. Chem*. **1975**, *106*, 1495–1497.
25. Hassan, M.M.; Othman, E.S.; Abass, M. 3-Acetyl-4-methylthioquinolin-2(1H)-one as useful synthon intermediate for synthesis of some new quinolinones. *Res. Chem. Intermed*. **2013**, *39*, 1209–1122.
26. Chaudhary, A.; Joshi, S.C.; Singh, R.V. Studies on Therapeutically Relevant Tin(II) and Lead(II) Complexes of Schiff Base Macrocyclic Ligands Containing Thiosemicarbazone Moiety. *Main Group Met. Chem*. **2004**, *27*, 59–70.
27. Ibrahim, S.S.; El-Gendy, Z.M.; Allimony, H.A.; Othman, E.S. New Quinolones and Naphthyridinones Bearing Heterocyclic Rings. *Chem. Papers* **1999**, *53*, 53–64.
28. Hasnaoui, A.; Lavergne, J.-P.; Viallefont, P. Condensation des composés β-dicarbonylés avec les thiosemicarbazides. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 301–306.
29. Hasnaoui, A.; Lavergne, J.-P.; Viallefont, P. Syntheses de nouvelles triazépines-1,2,4. *J. Heterocycl. Chem.* **1978**, *15*, 71–75.
30. Stanovnik, B.; Tišler, M. Zur Reaktion von 1,1,3,3-Tetraäthoxypropan mit Thiosemicarbaziden. *Naturwissenschaften* **1965**, *52*, 207.
31. Losse, G.; Farr, W. Synthese und Reaktionen der Heptriazinone. *J. Prakt. Chem*. **1959**, *8*, 298–305.
32. Ebnöther, A.; Jucker, E.; Rissi, E.; Rutschmann, J.; Schreier, E.; Steiner, R.; Süess, R.; Vogel, A. Über Azetidin-2,4-dione (Malonimide). *Helv. Chim. Acta* **1959**, *42*, 918–955.
33. Losse, G.; Hessler, W.; Barth, A. Ringschlussreaktionen mit Thiosemicarbaziden. *Chem. Ber*. **1958**, *91*, 150–157.
34. Seebacher, W.; Michl, G.; Weis, R. Synthesis of new triazepinethiones. *Tetrahedron Lett*. **2002**, *43*, 7481–7483.
35. Hassan, A.A.; Bebair, T.M.; El-Gamal, M. Synthesis of pyrazolylthiazole and pyrazolyl-1,2,4-triazepine derivatives. *J. Chem. Res*. **2014**, *38*, 27–31.
36. Aly, A.A.; Hassan, A.A.; El-Sheref, E.M.; Mohamed, M.A.; Brown, A.B. Conventional and Microwave Irradiation Assisted Synthesis of New 1,2,4-Triazepine-3-thiones. *J. Heterocycl. Chem.* **2008**, *45*, 521–526.
37. El-Helby, A.A.; Amin, M.A.; El-Sawah, M.M.; Bayoni, A.H.; El-Azab, A.S.; Sherbiny, F.F. Synthesis and Microbiological Testing of Some New Derivatives of Compounds Containing Active Methylene Group. *J. Saudi Chem. Soc*. **2006**, *10*, 77–93.
38. Abdel-Ghany, H.; Khodairy, A.; Moustafa, H.M. Novel Synthesis of Some Spiro Heterocycles Derived from 3-Hydroxy-3-(2-oxocyclohexyl)-indolin-2-one. *Synth. Commun.* **2000**, *30*, 1257–1268.
39. Kobayashi, M.; Tanaka, J.; Katori, T.; Marsuura, M.; Yamashita, M.; Kitagawa, I. The Absolute Stereostructure of Swinholide A, a Potent Cytotoxic Dimeric Macrolide from the Okinawan Marine Sponge *Theonella swinhoei*. *Chem. Pharm. Bull.* **1990**, *38*, 2409–2418.
40. Hosmane, R.S.; Bhadti, V.S.; Lim, B.B. Synthesis of a Novel Ring-Expanded Xanthine Analogue and Several Methyl or Benzyl Derivatives Containing the 5:7-Fused Imidazo[4,5-*e*][1,2,4]triazepine Ring System. *Synthesis* **1990**, 1095–1100.
41. Trafimova, L.A.; Zimin, M.O.; Shutalev, A.D. Thiocarbamate-based synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones. *J. Chem. Res.* **2017**, *41*, 149–156.
42. Fesenko, A.A.; Shutalev, A.D. Different modes of acid-catalyzed cyclization of 4-(γ-oxoalkyl)semicarbazide hydrazones: 7-membered versus 14-membered cyclic semicarbazones formation. *Tetrahedron* **2015**, *71*, 9528–9543.

43. Losse, G.; Uhlig, H. Neue Siebengliedrige Heterocyclen auf Thiosemicarbazidbasis. *Chem. Ber.* **1957**, *90*, 257–260.
44. Losse, G.; Wottgen, E.; Just, H. Substituierte 7gliedrige Heterocyclen mit mehreren Heteroatomen. *J. Prakt. Chem.* **1958**, *7*, 28–37.
45. Hutchins, R.O.; Hutchins, M.K. Reduction of C=N to CHNH by Metal Hydrides. In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Volume 8, pp. 25–78.
46. Hemmer, R.; Lürken, W. Amine. In *Houben-Weyl Methods of Organic Chemistry*; Thieme: Stuttgart, Germany, 1992; Volume E16d, pp. 646–1234.
47. Andersson, P.G.; Munslow, I.J. (Eds.) *Modern Reduction Methods*; Wiley-VCH Verlag: Weinheim, Germany, 2008.
48. Nugenta, T.C.; El-Shazly, M. Chiral Amine Synthesis - Recent Developments and Trends for Enamide Reduction, Reductive Amination, and Imine Reduction. *Adv. Synth. Catal.*, **2010**, *352*, 753–819.
49. Layer, R.W. The Chemistry of Imines. *Chem. Rev.*, **1963**, *63*, 489–510.
50. Tripathi, R.P.; Verma, S.S.; Pandey, J.; Tiwar, V.K. Recent development on catalytic reductive amination and applications. *Curr. Org. Chem.* **2008**, *12*, 1093–1115.
51. Hutchins, R.O.; Hutchins, M.K.; Crawley, M.L. Sodium Cyanoborohydride. In *e-EROS: Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: Weinheim, Germany, 2007; doi:10.1002/047084289X.rs059.pub2.
52. Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd ed.; Wiley-VCH: New York, NY, USA, 1997.
53. Lane, C.F. Sodium Cyanoborohydride—A Highly Selective Reducing Agent for Organic Functional Groups. *Synthesis* **1975**, *3*, 135–146.
54. Hutchins, R.O.; Natale, N.R. Cyanoborohydride. Utility and Applications in Organic Synthesis. A Review. *Org. Prep. Proced. Int*. **1979**, *11*, 201–246.
55. Borch, R.F.; Bernstein, M.D.; Durst, H.D. The Cyanohydridoborate Anion as a Selective Reducing Agent. *J. Am. Chem. Soc*. **1971**, *93*, 2897–2904.
56. 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).
57. Fesenko, A.A.; Grigoriev, M.S.; Shutalev, A.D. Nucleophile-Mediated Ring Expansion of 5-Acyl-substituted 4-Mesyloxymethyl-1,2,3,4-tetrahydropyrimidin-2-ones in the Synthesis of 7-Membered Analogues of Biginelli Compounds and Related Heterocycles. *J. Org. Chem.* **2017**, *82*, 8085−8110.
58. Fesenko, A.A.; Shutalev, A.D. 2,3-Dihydro-1*H*-1,3-diazepin-2-ones: synthesis and novel rearrangements into pyrrole derivatives. *Tetrahedron Lett.* **2014**, *55*, 1416−1420.
59. Fesenko, A.A.; Trafimova, A.A.; Shutalev, A.D. Synthesis of functionalized tetrahydro-1,3-diazepin-2-ones and 1-carbamoyl-1H-pyrroles *via* ring expansion and ring expansion/ring contraction of tetrahydropyrimidines. *Org. Biomol. Chem.* **2012**, *10*, 447−462.
60. Fesenko, A.A.; Shutalev, A.D. Nucleophile-mediated ring expansion of 4-chloromethyl- and 4-mesyloxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones to 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin- 2-ones: the effect of the leaving group and the substituent at C6. *Tetrahedron* **2011**, *67*, 6876−6882.
61. Fesenko, A.A.; Tullberg, M.L.; Shutalev, A.D. General approach to 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones via nucleophile-mediated ring expansion of tetrahydropyrimidines. *Tetrahedron* **2009**, *65*, 2344−2350.
62. Solovyev, P.A.; Fesenko, A.A.; Shutalev, A.D. A new synthesis of 4- or/and 6-CF3-containing hexahydro- and 1,2,3,4-tetrahydropyrimidin-2-ones. *J. Fluor. Chem.* **2016**, *182*, 28–33.
63. Fesenko, A.A.; Shutalev, A.D. A novel access to pyrido[4,3-d]pyrimidine scaffold via Staudinger/intramolecular aza-Wittig reaction of 5-acyl-4-(β-azidoalkyl)-1,2,3,4-tetrahydropyrimidin-2-ones. *Tetrahedron* **2014**, *70*, 5398–5414.
64. Fesenko, A.A.; Shutalev, A.D. Synthesis of γ-Azido-β-Ureido Ketones and their Transformation into Functionalized Pyrrolines and Pyrroles via Staudinger/aza-Wittig Reaction. *J. Org. Chem.* **2013**, *78*, 1190−1207.
65. Fesenko, A.A.; Dem'yachenko, E.A.; Fedorova, G.A.; Shutalev, A.D. A novel selective synthesis of β-isothiocyanato ketones through a Staudinger/aza-Wittig reaction of β-azido ketones. *Monatsh. Chem.* **2013**, *144*, 351−359.

66. Fesenko, A.A.; Solovyev, P.A.; Shutalev, A.D. A novel convenient synthesis of 5-acyl-1,2-dihydropyrimidin-2-ones via 4-trichloromethyl-1,2,3,4-tetrahydropyrimidin-2-ones. *Tetrahedron* **2010**, *66*, 940–946.
67. Fesenko, A.A.; Shutalev, A.D. Diastereoselective synthesis of 5-benzylthio- and 5-mercaptohexahydropyrimidin-2-ones. *Tetrahedron Lett.* **2007**, *48*, 8420–8423.
68. Shutalev, A.D.; Kurochkin, N.N. A new approach to the synthesis of Biginelli compounds. *Mendeleev Commun.* **2005**, *15*, 70–72.
69. Gribble, G.W.; Nutaitis, C.F. Sodium Borohydride in Carboxylic Acid Media. A Review of the Synthetic Utility of Acyloxyborohydrides. *Org. Prep. Proced. Int.* **1985**, *17*, 317–384.
70. Abdel-Magid, A.F.; Carson, K.G.; Harris, B.D.; Maryanoff, C.A.; Shah, R.D. Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures. *J. Org. Chem.* **1996**, *61*, 3849–3862.
71. Baxter, E.W.; Reitz, A.B. Reductive Aminations of Carbonyl Compounds with Borohydride and Borane Reducing Agents. *Org. React.* **2002**, *59*, 1–714.
72. Abdel-Magid, A.F.; Mehrman, S.J. A Review on the Use of Sodium Triacetoxyborohydride in the Reductive Amination of Ketones and Aldehydes. *Org. Proc. Res. Dev.* **2006**, *10*, 971–1031.