Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 447

www.rsc.org/obc

PAPER

Synthesis of functionalized tetrahydro-1,3-diazepin-2-ones and 1-carbamoyl-1*H*-pyrroles *via* ring expansion and ring expansion/ring contraction of tetrahydropyrimidines†

Anastasia A. Fesenko, Ludmila A. Trafimova and Anatoly D. Shutalev*

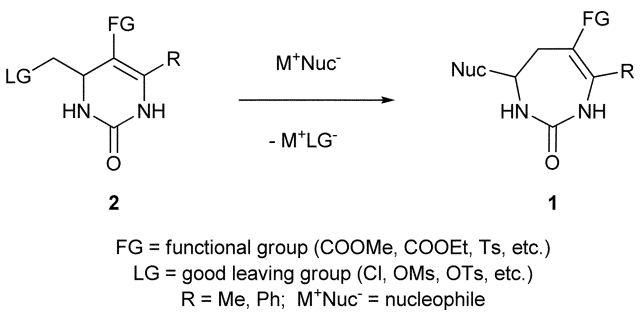
Received 28th July 2011, Accepted 26th September 2011
DOI: 10.1039/c1ob06284k

A general approach to 6-phenylthio-substituted 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones based on the ring expansion reaction of 1,2,3,4-tetrahydropyrimidin-2-ones under the action of nucleophiles has been developed. The first step of the synthesis was preparation of *N*-[(2-benzoyloxy-1-tosyl)ethyl]urea by three-component condensation of 2-benzoyloxyethanal, urea and *p*-toluenesulfinic acid. Nucleophilic substitution of the tosyl group in the obtained sulfone with sodium enolates of α-phenylthioketones followed by cyclization–dehydration, and debenzoylation gave 4-hydroxymethyl-5-phenylthio-1,2,3,4-tetrahydropyrimidin-2-ones which were transformed into the 4-mesyloxymethyl-derivatives. Treatment of the latter with nucleophilic reagents, such as NaCN, sodium diethyl malonate, PhSNa, MeONa, $NaBH_4$, sodium succinimide, or potassium phthalimide, afforded the target multi-functionalized diazepinones. The obtained 6-phenylthio-diazepinones and their 6-tosyl-substituted analogues were converted into 3-substituted 1-carbamoyl-1*H*-pyrroles under acidic conditions as a result of ring contraction. Effective one-pot synthesis of the latter from 4-mesyloxymethyl-pyrimidines was realized using a ring expansion/ring contraction sequence.

Introduction

Development of general approaches to rare heterocyclic scaffolds is important from the viewpoint of both synthetic and medicinal chemistry. We have been interested in straightforward synthesis of monocyclic tetrahydro-1*H*-1,3-diazepin-2-ones, particularly 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones, which remain practically unexplored.[1,2] The representatives of this class of heterocycles possess various biological activities. For example, 2-oxo-2,3,6,7-tetrahydro-1*H*-1,3-diazepine-5-carboxylates were demonstrated to be useful in the treatment of cardiovascular disorders.[3] The derivatives of 2,3,4,5-tetrahydro- and 2,3,4,7-tetrahydro-1*H*-1,3-diazepin-2-ones were shown to be powerful inhibitors of cytidine deaminase[2c,4] and potent inhibitors of metalloenzymes.[5]

The reported approaches to tetrahydro-1*H*-1,3-diazepin-2-ones are rather specific. The promising synthesis of 2-oxo-2,3,6,7-tetrahydro-1*H*-1,3-diazepine-5-carboxylates (**1** FG = COOR′) by ring expansion of 4-chloromethyl-substituted tetrahydropyrimidines **2** (FG = COOR′, LG = Cl) under the action of nucleophiles[3,6] (Scheme 1) is dramatically limited by the poor availability of starting materials. Only three tetrahydropyrimidines **2** (LG = Cl; EWG = COOMe, R = Me and EWG = COOEt, R = Me, Ph) have been prepared in extremely low to moderate yields (2–65%).[6b,6c]



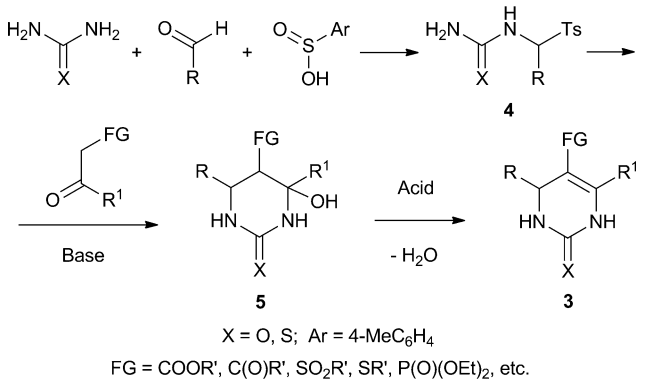
Scheme 1 Conversion of pyrimidines **2** to 6-functionalized 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones **1**.

Although the preparation of 5-functionalized 1,2,3,4-tetrahydropyrimidin-2-ones is well documented,[7,8] there are only rare examples of the synthesis of pyrimidines **2** or their possible precursors.[6b,6c,9] Obviously, the development of a general approach to tetrahydropyrimidinones of type **2** will give an access to various tetrahydrodiazepinones **1**.

Previously, we described a general three-step synthesis of 5-functionalized 1,2,3,4-tetrahydropyrimidin-2-ones/thiones **3** based on the reaction of α-tosyl-substituted *N*-alkylureas and *N*-alkylthioureas **4** with enolates of α-substituted ketones followed by acid-catalyzed dehydration of the obtained 4-hydroxyhexahydropyrimidin-2-ones/thiones **5** (Scheme 2).[10]

Department of Organic Chemistry, Moscow State Academy of Fine Chemical Technology, 86 Vernadsky Avenue, 119571, Moscow, Russian Federation. E-mail: shutalev@orc.ru; Fax: +7-495-9368909; Tel: +7-495-9368910

† Electronic supplementary information (ESI) available: IR and NMR (^{1}H and ^{13}C) spectra of all obtained compounds, detailed procedure for multigram scale syntheses of 2-benzoyloxyethanal (**8**) and *N*-[(2-benzoyloxy-1-tosyl)ethyl]urea (**9**). See DOI: 10.1039/c1ob06284k



Scheme 2 General synthesis of 5-functionalized 1,2,3,4-tetrahydropyrimidin-2-ones/thiones **3**.

Starting sulfones **4** were prepared by three-component condensation of aldehyde, *p*-toluenesulfinic acid and (thio)urea in water at room temperature followed by filtration of the precipitate.

This synthesis is flexible and gives easy access to 1,2,3,4-tetrahydropyrimidin-2-ones/thiones bearing various functional groups at C5 and substituents at C4 and C6 including functionalized ones. Using this method, we have prepared 4-mesyloxymethyl-, 4-tosyloxymethyl- and 4-chloromethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones (**2** LG = OMs, OTs, Cl; FG = Ts) and demonstrated that they can serve as precursors for tetrahydrodiazepinones (**1** FG = Ts).[11]

In continuation of our research in this area, we describe here the synthesis of 4-mesyloxymethyl-5-phenylthio-substituted 1,2,3,4-tetrahydropyrimidin-2-ones and their reaction with various nucleophiles affording novel 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones as a result of ring expansion. Before our studies this transformation was demonstrated only for substrates bearing electron-withdrawing groups at C5, such as an alkoxycarbonyl group (**2** FG = COOR′)[3,6] or a tosyl group (**2** FG = Ts).[11] We envisage that the introduction of the electron-donating PhS group at C5 of the starting pyrimidinones can clarify some peculiarities of the mechanism of this transformation and can be of value for other similar reactions of one-carbon atom ring expansion.[3,4b,6,12] We also describe acid-catalyzed ring contraction of some obtained diazepines into 3-functionalized 1-carbamoyl-1*H*-pyrroles and the synthesis of the latter from tetrahydropyrimidines using a one-pot ring expansion/ring contraction sequence.

Results and discussion

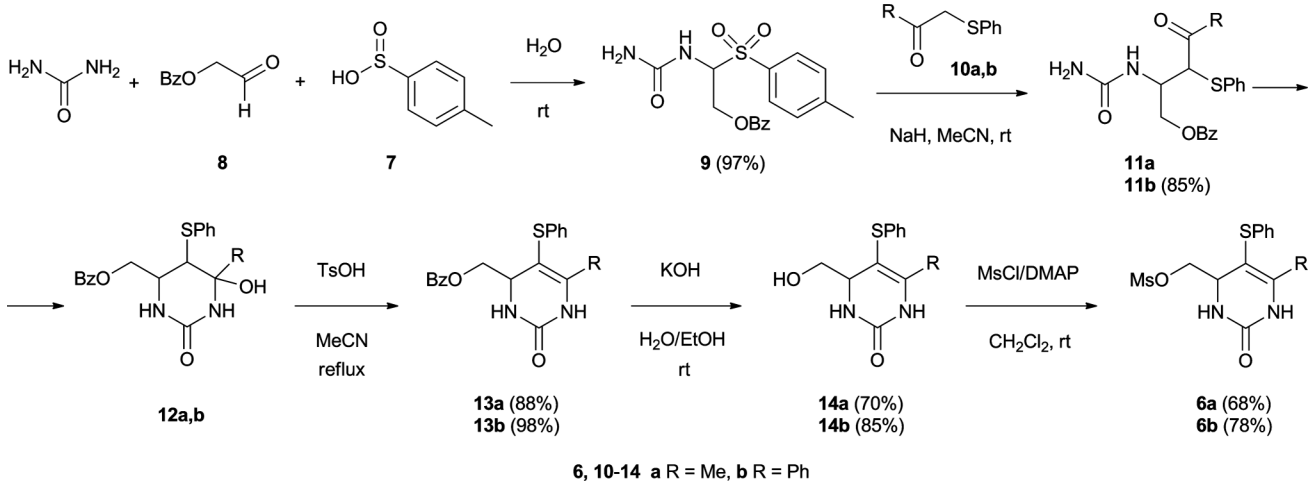
Synthesis of diazepine precursors

Key intermediates for the diazepinone synthesis, 4-mesyloxymethyl-5-phenylthio-substituted 1,2,3,4-tetrahydropyrimidin-2-ones **6a,b** were prepared as outlined in Scheme 3.

The assembly of tetrahydropyrimidine ring comprised three steps. The first step was a three-component condensation of 2-benzoyloxyethanal (**8**), *p*-toluenesulfinic acid (**7**) and urea in water at room temperature that provided access to sulfone **9** in 97% yield on a multi-gram scale.[13]

The second step involved nucleophilic substitution of the tosyl group in urea **9** by the enolates of α-phenylthio-substituted ketones **10a,b** generated by reacting corresponding CH-acids with NaH in dry MeCN. With phenylthioacetone **10a** this substitution proceeded smoothly in MeCN at rt over 8 h, and the obtained product (β-oxoalkylurea **11a** or hydroxypyrimidine **12a**) was dehydrated without isolation after the addition of TsOH (1.33 equiv.) to the reaction mixture followed by refluxing for 2 h to give 4-benzoyloxymethyl-pyrimidine **13a** in 88% yield. This one-pot methodology of tetrahydropyrimidine synthesis failed when phenylthioacetophenone **10b** was used as a starting material. The addition of TsOH (1.5 equiv.) and refluxing of the reaction mixture formed after completion of the reaction of urea **9** with sodium enolate of **10b** for 4 h led to formation of considerable amounts of side products, which significantly decreased the yield and purity of tetrahydropyrimidine **13b**. This compound was successfully prepared in two steps in 83% overall yield. The reaction of **9** with the sodium enolate of **10b** (MeCN, rt, 8 h) gave β-oxoalkylurea **11b** as a mixture of two diastereomers (78 : 22) which was dehydrated by refluxing for 4 h in MeCN in the presence of TsOH (0.5 equiv.).

The benzoyl protection in **13a,b** was removed using an EtOH–H_2O solution of KOH (1.8 equiv.) (rt, 3 h) to give hydroxymethyl-tetrahydropyrimidines **14a** and **14b** in 70 and 85% yields, respectively. Previously we have shown[11b] that the mesyloxy group



Scheme 3 Synthesis of 5-phenylthio-substituted 4-mesyloxymethyl-1,2,3,4-tetrahydropyrimidin-2-ones **6a,b**.

Table 1 Reaction of mesyloxymethyl-pyrimidines **6a,b** with NaCN (1.49–1.69 equiv.)

Entry	Starting material	Catalyst[a]	Solvent	Conc. of **6** (mol L^{-1})	Reaction conditions	Conversion of **6**[b] (%)	Product	Purity of **15**[c] (%)	Yield[d] (%)
1	**6a**	18-crown-6	MeCN	0.033	reflux, 5 h	73	**15a**	—	—
2	**6a**	18-crown-6	MeCN	0.050	reflux, 5 h	100	**15a**	59	55
3	**6a**	18-crown-6	MeCN	0.067	reflux, 3 h	100	**15a**	52	—
4	**6a**	18-crown-6	MeCN	0.250	reflux, 3.25 h	100	**15a**	32	—
5	**6a**	—	DMF	1.429	rt, 3 h	49	**15a**	—	—
6	**6a**	—	DMF	2.500	rt, 6.7 h	100	**15a**	39	(30)
7	**6b**	18-crown-6	MeCN	0.033	reflux, 4 h	100	**15b**	70	63
8	**6b**	18-crown-6	MeCN	0.067	reflux, 3.2 h	100	**15b**	38	—
9	**6b**	18-crown-6	MeCN	0.200	reflux, 3 h	100	**15b**	22	15
10	**6b**	—	DMF	1.000	rt, 2.5 h	87	**15b**	—	—
11	**6b**	—	DMF	2.500	rt, 7 h	100	**15b**	35	(33)

[a] 0.1–0.2 equiv. [b] According to ^{1}H NMR spectroscopy of the crude isolated material. [c] Purity was estimated as ratio of the expected integral intensity of the aromatic protons region (5 H for **15a**, 10 H for **15b**) to the observed integral intensity in this region in the ^{1}H NMR spectrum of the crude product multiplied by 100. [d] Isolated yields after column chromatography. The yields in parenthesis were determined by ^{1}H NMR spectroscopy with 1,4-dioxane as an internal standard.

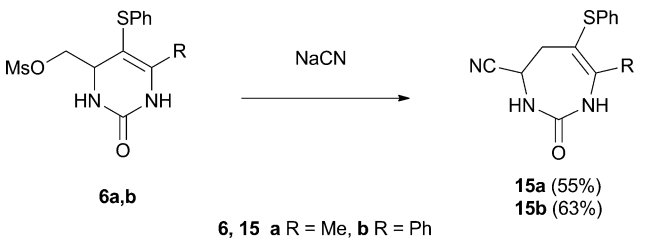
is the best good-leaving group into which the hydroxy group can be transformed. Under optimized reaction conditions, 4-mesyloxymethyl-tetrahydropyrimidines **6a,b** were prepared by the reaction of **14a,b** with MsCl in the presence of DMAP in CH_2Cl_2 at room temperature. The ratio of pyrimidine/MsCl/DMAP was 1 : 1.2 : 1.4 for **14a** and 1 : 1.5 : 2 for **14b**.[14] A slightly greater excess of reagents was used with **14b** to reduce the reaction time (2 h 20 min instead of 5 h 40 min at a **14b**/MsCl/DMAP ratio of 1 : 1.2 : 1.4).[15] The yields of **6a** and **6b** after crystallization were 68 and 78%, respectively. Thus, the 4-mesyloxymethyl-5-phenylthio-substituted pyrimidines **6a,b** were obtained from urea **9** in 42–56% overall yields.

The noticeable spectral characteristic of 6-methyl-pyrimidinones **6a**, **13a**, and **14a** is the long-range coupling between protons 4-H and 6-CH_3 ($^5J_{4\text{-H},6\text{-CH}3}$ = 0.8–1.0 Hz) which, together with the value of vicinal coupling between 4-H and $N_{(3)}H$ ($^3J_{N(3)H,4\text{-H}}$ = 2.7 Hz), demonstrates that the orientation of the substituent at the C4-position of the pyrimidine ring is pseudo equatorial (in DMSO-d_6 solution). Close values of couplings $^3J_{N(3)H,4\text{-H}}$ = 2.4–2.8 Hz for 6-phenyl-substituted pyrimidinones **6b**, **13b**, and **14b** show that the orientation of the substituent at C4 is the same. Thus, the conformation of pyrimidinones **6**, **13**, and **14** significantly differs from that previously described for other 5-functionalized tetrahydropyrimidinones.[11,16] Generally, ^{1}H NMR spectra of the latter show values of vicinal coupling $^3J_{N(3)H,4\text{-H}}$ in the range of 3.4–3.9 Hz and no long-range coupling $^5J_{4\text{-H},6\text{-CH3}}$ (for 6-methyl-pyrimidinones).

Synthesis of diazepinones *via* ring expansion

We studied the reaction of one-carbon atom ring expansion of 4-mesyloxymethyl-pyrimidines **6a,b** under the action of various *C*-, *N*-, *S*-, *H*- and *O*-nucleophiles. Since the phenyl-group at the C6-position of the pyrimidine ring significantly complicates the reaction with all nucleophiles,[11] we focused on the reactivity of 6-phenylpyrimidine **6b**, and optimal conditions found for this starting material were used for 6-methylpyrimidine **6a**.

Sodium diethyl malonate and sodium cyanide were used as *C*-nucleophiles. With both nucleophiles the reactions proceeded under more forcing conditions compared with the corresponding 5-tosyl-substituted analogues.[11] Selected experimental data for the reaction of **6a,b** and NaCN giving 4-cyano-6-phenylthio-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones **15a,b** (Scheme 4) are summarized in Table 1.



6a,b

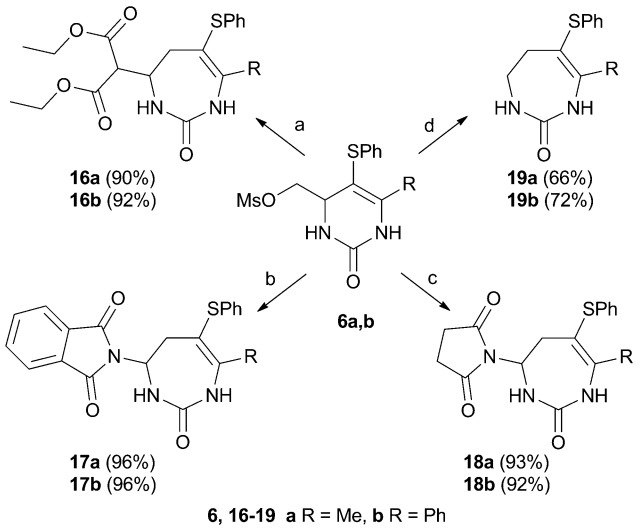
15a (55%)
15b (63%)

6, 15 **a** R = Me, **b** R = Ph

Scheme 4 Synthesis of 4-cyano-6-phenylthio-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones **15a,b** by the reaction of mesyloxymethyl-pyrimidines **6a,b** with NaCN.

The ring expansion reaction of **6a,b** under the action of NaCN (1.49–2.01 equiv.) was carried out in refluxing MeCN,[17] THF or 1,4-dioxane for 3–9 h in the presence of 18-crown-6 (0.10–0.22 equiv.). Under all studied conditions an amount of unidentified side products always formed along with diazepinones **15a,b** as detected by ^{1}H NMR spectra of the isolated crude materials. The characteristic feature of these spectra was an increase in the relative integral intensity of the aromatic protons region (6.70–7.70 ppm). Purity of the isolated diazepinones **15a,b** strongly depended on the starting concentration of **6a,b**. At higher concentrations the amount of side products increased (entries 2–4 for **6a**; entries 7–9 for **6b**). Polarity of solvent, reaction temperature, amounts of NaCN and 18-crown-6 caused only insignificant changes in the purity of diazepinones **15a,b**. In dry DMF the reaction of **6a,b** with NaCN was complete in about 7 h at room temperature (entries 6 and 11). However, under these conditions side reactions similar to those proceeding in MeCN, THF or 1,4-dioxane were observed. Under optimal conditions 4-cyano-substituted diazepinones **15a** (entry 2) and **15b** (entry 7) were isolated in 55 and 63% yields, respectively, after column chromatography.

The reaction of **6b** with sodium diethyl malonate (1.25 equiv.) affording diazepinone **16b** (Scheme 5) proceeded very slowly in dry MeCN at room temperature, and according to TLC a considerable amount of starting material remained in the reaction mixture after



Scheme 5 Synthesis of 6-phenylthio-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones **16–19a,b** by the reaction of mesyloxymethyl-pyrimidines **6a,b** with sodium malonate, potassium phthalimide, sodium succinimide, and $NaBH_4$. *Reagents and conditions*: a) $CH_2(COOEt)_2$, NaH, THF, rt, 5 h; b) potassium phthalimide, MeCN, reflux, 0.5–1.7 h; c) succinimide, NaH, THF, reflux, 3.75–4 h; d) $NaBH_4$, THF, reflux, 1.8–4.2 h.

8 h. Some unreacted **6b** was observed (TLC) after 6 h 40 min even after the amount of nucleophile was increased to 1.80 equiv. No starting material was detected (TLC) in the reaction mixture (**6b**/sodium diethyl malonate at the ratio of 1.00 : 1.25) in refluxing dry MeCN for 40 min, however some side products were formed. In order to avoid this we increased the basicity of the reaction media using a less polar solvent such as dry THF. In THF the reaction of 4-mesyloxymethyl-pyrimidines **6a,b** with sodium diethyl malonate (1.26–1.29 equiv.) proceeded smoothly at room temperature in 5 h to give diazepinones **16a** and **16b** in 90 and 92% yields, respectively.

Pyrimidinones **6a,b** readily reacted with *N*-nucleophiles. With potassium phthalimide (1.5 equiv.) the expected products **17a,b** formed in refluxing MeCN for 0.5–1.7 h in 96% yield. When **6b** was refluxed in dry MeCN in the presence of sodium succinimide (1.5 equiv.) generated by treatment of succinimide with NaH, the formation of some side products was observed. The reaction of **6a,b** with sodium succinimide proceeded smoothly in THF at reflux (3.75–4 h) to give products **18a,b** in 93 and 92% yields, respectively.

Sodium borohydride acted as a nucleophile, mediating the ring expansion of pyrimidines **6a,b** in THF at reflux for 1.8–4.2 h to obtain 4-unsubstituted diazepinones **19a** and **19b**, which were isolated using column chromatography in 66 and 72% yields, respectively.

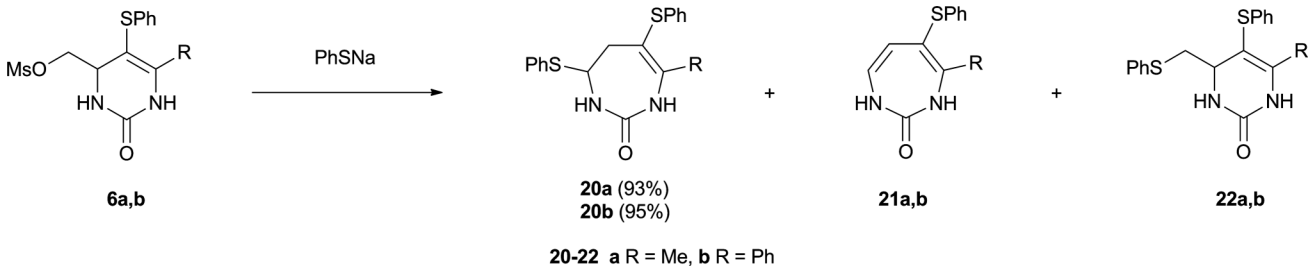
It is noteworthy that the reactions of **6a,b** with nucleophiles as described above gave only products of ring expansion, the corresponding tetrahydro-1*H*-1,3-diazepin-2-ones **15–19**. The products of direct nucleophilic substitution of the leaving group (1,2,3,4-tetrahydropyrimidin-2-ones) were not observed. However, the reaction of **6a,b** with PhSNa generated by treatment of PhSH with NaH gave three different products: tetrahydrodiazepinones **20a,b**, dihydrodiazepinones **21a,b**, and tetrahydropyrimidinones **22a,b** (Scheme 6). Under optimal conditions the total amount of side products (compounds **21a,b** and **22a,b**) did not exceed 5% according to ^{1}H NMR data of isolated crude materials (Table 2). Under these conditions the yields of 4-phenylthio-substituted diazepinones **20a** and **20b** were 93 and 95%, respectively.

In contrast to the previously studied reaction of ethyl 4-chloromethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate and 6-methyl-4-mesyloxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one with PhSNa with or without PhSH,[11,18] with **6a,b** formation of the products of direct nucleophilic substitution (compounds **22a,b**) proceeded even without large excesses of PhSH. In a polar solvent (MeCN), a temperature increase (Table 2, entry 14 *vs.* entries 13 and 3) and a greater excess of nucleophile (entry 12 *vs.* entry 13) favored this process. No product of direct substitution was detected even in the presence of small amounts of PhSH without excess of nucleophile in a less polar solvent (THF) at reflux (entry 5); however, some amount of starting material was recovered. At

Table 2 Reaction of mesyloxymethyl-pyrimidines **6a,b** with PhSH in the presence of NaH

Entry	Starting material	Molar ratio of **6**/PhSH/NaH	Solvent	Reaction conditions	Product distribution[a] (%)				Yield of **20**[b] (%)
					6	**20**	**21**	**22**	
1	**6a**	1 : 1.20 : 1.20	THF	reflux, 2 min	—	95	1	4	93
2	**6a**	1 : 1.19 : 1.19	THF	reflux, 1 h	—	89	5	6	—
3	**6a**	1 : 1.13 : 1.10	MeCN	reflux, 40 min	—	53	6	41	—
4	**6a**	1 : 1.29 : 1.25	THF	rt, 4 h	—	90	4	6	—
5	**6b**	1 : 1.12 : 1.03	THF	reflux, 1 h	8	92	—	—	—
6	**6b**	1 : 1.28 : 1.28	THF	rt, 8 h	—	89	4	7	—
7	**6b**	1 : 1.20 : 1.20	THF	reflux, 1 h	—	77	21	2	—
8	**6b**	1 : 2.09 : 2.07	THF	reflux, 1 h	—	44	56	—	—
9	**6b**	1 : 1.39 : 1.24	THF	rt, 1 h 40 min	—	82	—	18	—
10	**6b**	1 : 3.12 : 3.09	THF	reflux, 3 min	—	77	23	—	—
11	**6b**	1 : 3.13 : 3.11	THF	reflux, 1 h	—	51	49	—	—
12	**6b**	1 : 1.10 : 1.03	MeCN	reflux, 50 min	—	95	5	—	—
13	**6b**	1 : 1.12 : 1.10	MeCN	reflux, 30 min	—	66	10	24	—
14	**6b**	1 : 1.09 : 1.07	MeCN	rt, 3 h	23	77	—	—	—
15	**6b**	1 : 1.22 : 1.21	1,4-dioxane	reflux, 1 h	—	49	38	13	—
16	**6b**	1 : 1.20 : 1.20	THF	reflux, 1 min	—	95	2	3	95

[a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield.



Scheme 6 Synthesis of 4,6-diphenylthio-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones **20a,b** by the reaction of mesyloxymethyl-pyrimidines **6a,b** with PhSNa.

room temperature in THF a greater excess of PhSH caused an increase in the amount of **22b** (entry 4 *vs.* entry 9).

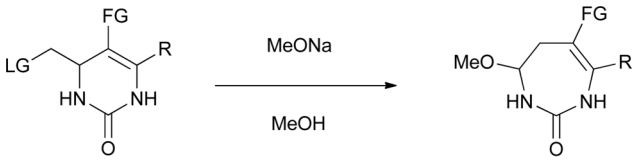
The structure of compounds **22a,b** was determined by comparison of their ^{1}H NMR spectra with those reported previously for ethyl 4-phenylthiomethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate and 6-methyl-4-phenylthiomethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one.[18]

Unexpectedly, other side products were detected in the reaction of **6a,b** with PhSNa. We suppose that these products (5-phenylthio-2,3-dihydro-1*H*-1,3-diazepin-2-ones **21a,b**)[19] formed as a result of elimination of PhSH from **20a,b** under the reaction conditions. The amount of **21a,b** increased with prolongation of the reaction time both at room temperature (entry 9 *vs.* entry 6) and reflux (entry 16 *vs.* entry 7; entry 10 *vs.* entry 11; entry 1 *vs.* entry 2), an increase in the amount of nucleophile (entry 12 *vs.* entry 13; entry 7 *vs.* entries 8 and 11) and with a rise in temperature (entry 7 *vs.* entry 15). The tendency for elimination of PhSH affording the corresponding dihydrodiazepinone is stronger for 7-phenyl-substituted tetrahydrodiazepinone **20b** than for its 7-methyl-substituted analogue **20a**.

The dihydrodiazepinone structure of **21b** was determined on the basis of its ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum exhibited a doublet of doublets at 5.16 ppm assigned to 6-H ($^3J_{6\text{-H},7\text{-H}} = 8.2$ Hz, $^4J_{6\text{-H},N(1)H} = 1.2$ Hz), a doublet of doublets at 5.85 ppm due to 7-H ($^3J_{7\text{-H},6\text{-H}} = 8.2$ Hz, $^3J_{7\text{-H},N(1)H} = 5.8$ Hz), a doublet at 8.12 ppm due to $N_{(3)}H$ ($^4J_{N(3)H,N(1)H} = 2.2$ Hz), and a doublet of doublets of doublets at 8.18 ppm corresponding to $N_{(1)}H$. In the ^{13}C NMR spectrum the signals of the dihydrodiazepinone ring were observed at 164.5 (C-2), 143.7 (C-4), 129.2 (C-7), 114.6 (C-6), and 112.6 (C-5) ppm. The ^{1}H and ^{13}C NMR spectral characteristics for **21a** were similar.

4-Methoxy-6-phenylthio- and 4-methoxy-6-tosyl-substituted diazepinones **24a–d** were obtained in the reaction of pyrimidines **6a,b** and **23a,b** with MeONa (2.5 equiv.) in MeOH (Scheme 7).

5-Tosyl-substituted pyrimidinones **23a,b** were prepared as described previously.[11] Experimental data obtained with MeONa as a nucleophile clearly demonstrated that the reaction rate strongly depends on the functional group at C5, the substituent at C6 and the leaving group **LG**. The rate of ring expansion increased with 6-methyl-substituted substrates compared with their 6-phenyl-substituted counterparts. 6-Methyl-pyrimidine **6a** reacted with MeONa in MeOH for 2 h at room temperature to give diazepinone **24a** in 97% yield, while under these conditions the reaction of 6-phenyl-pyrimidine **6b** was complete after only 4 h to provide diazepinone **24b** in the same yield. The reaction rate increased with the change of functional group at C5 from electron-



23 a FG = Ts, R = Me, LG = OMs; **b** FG = Ts, R = Ph, LG = Cl
24 a FG = SPh, R = Me; **b** FG = SPh, R = Ph; **c** FG = Ts, R = Me; **d** FG = Ts, R = Ph

Scheme 7 Synthesis of 4-methoxy-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones **24a–d** by the reaction of mesyloxymethyl-pyrimidines **6a,b**, **23a,b** with MeONa in MeOH.

donating (PhS) to electron-withdrawing (Ts). In contrast to **6a**, the reaction of 5-tosyl-substituted pyrimidine **23a** was complete in 50 min to give diazepinone **24c** in 95% yield. Changing the leaving group from Cl to MsO also increased the reaction rate. Indeed, at room temperature chloromethyl-substituted pyrimidine **23b** reacted with MeONa in MeOH very slowly: after 4 h of reaction a significant amount of starting material remained in the reaction mixture (according to TLC). However, at reflux this reaction proceeded in 2 min affording 4-methoxy-diazepinone **24d** in 93% yield.

The structure of the obtained diazepinones **15–20a,b** and **24a–d** was confirmed by NMR spectroscopic data as described elsewhere.[11] For example, characteristic features of ^{1}H NMR spectra of **15–16a,b**, **20a,b** and **24a–d** included a high geminal coupling constant between 5-H(A) and 5-H(B) (14.8–16.7 Hz), a rather high vicinal coupling constant between $N_{(3)}H$ and 4-H (4.6–7.0 Hz), and long-range coupling between 5-H(A) and 7-CH_3 for 7-methyl-diazepinones (1.5–1.7 Hz). Additional spectroscopic data, such as a doublet in the range of 3.63–3.76 ppm ($^3J_{CH,4\text{-H}} =$ 8.8–9.9 Hz) for the methine proton in $CH(COOEt)_2$ observed for compounds **16a,b**, and two multiplets (each 2H) in the ranges of 3.14–3.33 and 2.38–2.56 ppm for 4-H and 5-H observed for **19a,b**, also confirmed the diazepine structure of the products obtained. Formation of the diazepine ring for compounds **17–18a,b** is unambiguously confirmed by their ^{1}H NMR spectra in which long-range couplings between 5-H(B) and N(3)H (1.2–1.5 Hz) and between 5-H(A) and 7-CH_3 (1.2–1.3 Hz for **17a** and **18a**) were observed.

The values of coupling constants between $N_{(3)}H$, 4-H, 5-H(A), and 5-H(B) ($^3J_{4\text{-H},5\text{-H(A)}} = 1.4$–$3.3$, $^3J_{4\text{-H},5\text{-H(B)}} = 4.8$–$7.4$, and $^3J_{4\text{-H},N(3)H} =$ 4.6–7.0 Hz) have proved that tetrahydrodiazepinones **15–16a,b**, **20a,b**, **24a–d** exist predominantly in a puckered conformation with

a pseudo axial orientation of the substituent at C4 (in DMSO-d_6). The conformation of diazepinones **17a,b** and **18a,b** formed in the reaction of **6a,b** with *N*-nucleophiles differs in the orientation of the substituent at C4 which is pseudo equatorial. This is in agreement with the lower values of the geminal coupling constant between 5-H(A) and 5-H(B) ($^2J_{5\text{-H(A)},5\text{-H(B)}}$ = 13.7–14.3 Hz), the high values of the vicinal coupling constant between 4-H and 5-H(A) ($^3J_{5\text{-H(A)},4\text{-H}}$ = 10.5–11.1 Hz), and the low vicinal coupling constant between $N_{(3)}H$ and 4-H ($^3J_{N(3)H,4\text{-H}}$ = 0.8–1.3 Hz), which were observed in their ^{1}H NMR spectra in DMSO-d_6.

Plausible mechanism of the ring expansion reaction

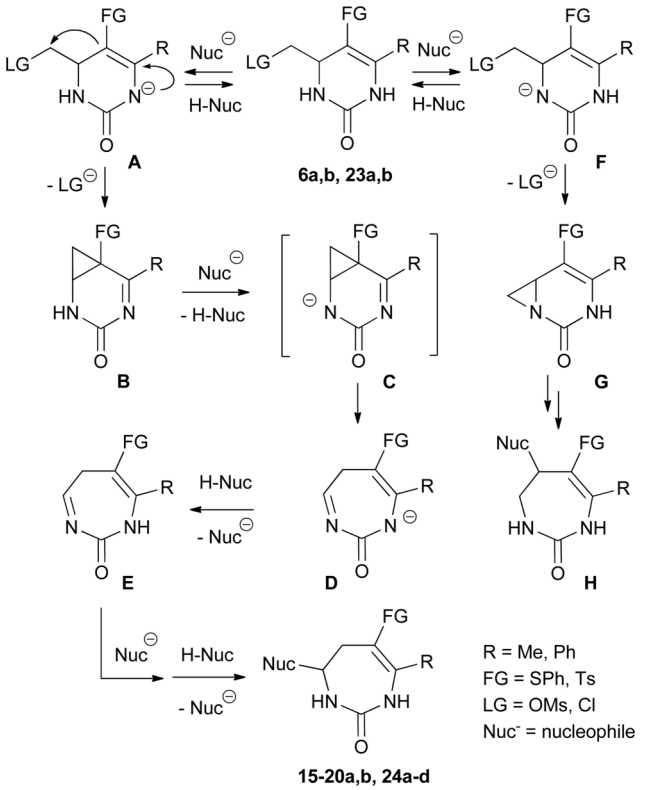
Previously it was demonstrated that nitrogen-containing heterocycles (1,4-dihydropyridines,[12d,k,m–o] 1,2,3,4-tetrahydropyrimidines,[6] 9,10-dihydroacridines[12a,b]) with HN–C═C–C–C–LG moiety (LG = good leaving group, *e.g.* Cl, OTs, OMs) underwent one-carbon atom ring expansion reactions under the action of nucleophiles. It was shown that the basic properties of the nucleophiles played a significant role for these transformations which started *via* proton abstraction from the NH group. The formed anion was supposed to undergo intramolecular nucleophilic substitution of the leaving group to give corresponding bicyclic cyclopropane intermediates followed by the formation of the final products.

Recently, we studied the ring expansion reaction of pyrimidinones **2** (Scheme 1, R = Me; FG = Ts, COOEt; LG = Cl, OMs) under the action of strong non-nucleophilic bases (NaH, DBU)[11a,20] or PhSNa in the presence of PhSH.[18] The data obtained was in good agreement with the above route of the reaction.

The detailed mechanism of formation of tetrahydrodiazepinones **15–20** and **24** is shown in Scheme 8. Proton abstraction from the more acidic $N_{(1)}H$ group[21] under the action of a nucleophile initiates the reaction. The obtained anions **A** give bicyclic cyclopropane intermediates **B**. We suppose that further transformation of **B** into diazepinones under basic nucleophilic conditions may proceed *via* three different pathways: NH deprotonation followed by ring expansion, electrocyclic opening of the cyclopropane ring or nucleophilic attack on the bridge-head carbon atom bound with nitrogen. *Ab initio* calculations (B3LYP/6-31+G(d,p))[22] performed for the reaction of 2,4-diazabicyclo[4.1.0]hept-4-en-3-one with hydride anion as a model reaction showed that the first pathway is preferable.[23] Thus, deprotonation of **B** results in formation of extremely unstable anions **C**, followed by spontaneous ring expansion to give diazepine anions **D**. Protonation of anions **D** and addition of the nucleophile to the obtained acylimines **E** give the final products.

The proposed mechanism is in good agreement with the experimental data described above. Indeed, an increase in the reaction rate with the change from an electron-donating group (SPh) to an electron-withdrawing group (Ts) at C5 of the starting pyrimidines **6**, **23** can be explained by better stabilization of anions **A** and **D** with Ts compared with the SPh substituent.

An alternative pathway of tetrahydropyrimidine ring expansion could include proton abstraction from $N_{(3)}H$ to give anions **F** followed by formation of aziridine intermediates **G**. However, ring opening of aziridines **G** under the action of nucleophiles would lead to attachment of the nucleophile to C5 to give compounds **H** rather than to C4 as was observed. Thus, reaction pathway *via* the formation of aziridine intermediates can be excluded.



Scheme 8 A plausible pathway for transformation of **6a,b**, **23a,b** into diazepinones **15–20a,b**, **24a–d**.

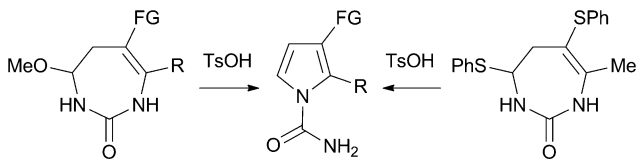
To confirm the proposed mechanism, we attempted to detect the intermediates in the reactions of 4-mesyloxymethyl-pyrimidines **6a,b** and **23a** with NaCN and potassium phthalimide using ^{1}H NMR spectroscopy. A solution of **6a,b** or **23a** in DMSO-d_6 was treated with the nucleophiles (1.3–1.4 equiv.) in an NMR tube and the progress of the reactions was monitored by ^{1}H NMR at 25 °C. The reactions of 5-tosylpyrimidine **23a** with both nucleophiles proceeded very quickly and completed in 20–25 min to give the corresponding diazepinones.[11b] After 7–9 min of reaction, only small amounts of starting material (6–8%) were observed. 5-Phenylthiopyrimidines **6a,b** reacted with the nucleophiles much more slowly and all the reactions completed in 24 h to give diazepinones **15a,b** and **17a,b**. After 30 min, the ^{1}H NMR spectra showed 16–24% and 64–67% conversions for the reactions of **6a** and **6b**, respectively. No intermediates were detected in all NMR experiments described above, because of their short lifetimes under experimental conditions.

According to the proposed mechanism (Scheme 8), conversion of pyrimidinones **6a,b**, **23a,b** into diazepinones **15–20a,b**, **24a–d** can be divided into two consecutive sets of reactions: the first set is the pyrimidine ring expansion determined by the basicity of the nucleophile resulting in acylimines **E**, and the second one is the nucleophilic addition to acylimines **E** determined by the nucleophilicity of the nucleophile to give the final products. Clearly, the first set of reactions can proceed without addition of nucleophile in the presence of an appropriate non-nucleophilic base (*e.g.*, DBU). To confirm this hypothesis, a solution of **6a,b** in DMSO-d_6 was treated with DBU (2.5–4 equiv.) in an NMR tube and the progress of the reactions was monitored by ^{1}H NMR spectroscopy at 25 °C. The reaction of **6b** proceeded very quickly

and after 9 min only 8% of starting material was observed. The ^{1}H NMR spectrum of the reaction mixture showed signals from three new compounds: dihydrodiazepinone **21b** (65%), the conjugated base of **21b** (13%),[24] and bicyclic intermediate **B** (Scheme 8, FG = SPh, R = Ph) (14%).[25] After 2 days, the ^{1}H NMR spectrum showed only compound **21b**. Evidently, the formation of the latter can be explained by DBU-promoted ring expansion reaction of **6b** to give the corresponding acylimine **E** (Scheme 8). In the absence of nucleophiles, the latter affords **21b** as a result of acylimine–enamide tautomerization. The reaction of **6a** with DBU proceeded similarly to that of **6b**, however, more slowly. The final product detected by ^{1}H NMR was dihydrodiazepinone **21a** only. After 14 min and 1.5 h from the beginning of the reaction, the ^{1}H NMR spectra showed the presence of starting material, **21a**, the conjugated base of **21a**, and bicyclic intermediate **B** (FG = SPh, R = Me)[26] in the ratios of 89 : 7 : 2 : 2 and 54 : 29 : 7 : 10, respectively.

Synthesis of 1-carbamoylpyrroles *via* ring contraction

Due to the low availability of 2,3,4,5-tetrahydro-1,3-1*H*-diazepin-2-ones their chemistry has remained poorly explored. Only two tetrahydrodiazepine-5-carboxylates were reported to undergo an acid-catalyzed transformation into 1-carbamoyl-1*H*-pyrrole-3-carboxylates *via* ring contraction.[6c] In order to develop the synthesis of 1-carbamoyl-3-phenylthio-1*H*-pyrroles and 1-carbamoyl-3-tosyl-1*H*-pyrroles we studied the reactivity of 4-phenylthio- and 4-methoxy-diazepinones **20a**, **24a–d** under acidic conditions (Scheme 9, Table 3).



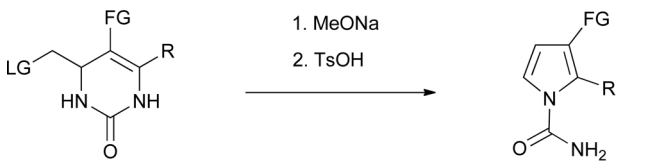
24a-d **25a-d** (78-96%) **20a**

25 a FG = SPh, R = Me; **b** FG = SPh, R = Ph; **c** FG = Ts, R = Me; **d** FG = Ts, R = Ph

Scheme 9 Acid-catalyzed ring contraction of diazepinones **20a**, **24a–d** to 1-carbamoyl-1*H*-pyrroles **25a–d**.

Firstly, we studied the ring contraction reactions of **24a–d** in refluxing MeOH in the presence of TsOH. 7-Methyl-6-phenylthio-diazepinone **24a** was smoothly converted into pyrrole **25a** in 0.5 h in 89% yield (entry 1). Under similar conditions, reactions of **24b–d** proceeded more slowly and gave side products. For example, in the case of **24b**, a mixture of starting material, pyrrole **25b** and dihydrodiazepinone **21b** in a ratio of 14 : 61 : 25, respectively, was obtained (according to the ^{1}H NMR spectrum) (entry 3). Use of EtOH (95%) instead of MeOH in the ring contraction reaction was more effective. Thus, 1-carbamoylpyrroles **25b–d** were prepared from **24b–d** in 78, 88 and 96% yields respectively in refluxing EtOH in the presence of TsOH (entries 4, 6 and 7). Pyrrole **25a** was also obtained from 4-phenylthio-substituted diazepinone **20a** in 84% yield using EtOH as a solvent (entry 2). We suppose that the better result achieved with EtOH compared to that with MeOH can be explained by the presence of water in EtOH. It was confirmed by the smooth transformation of **24b** into pyrrole **25b** in refluxing 95% aqueous MeOH (entry 5).

The data obtained were used for efficient preparation of pyrroles **25a–d** directly from pyrimidines **6a,b**, **23a,b** without isolation of intermediate methoxydiazepines **24a–d** *via* the ring expansion/ring contraction sequence (Scheme 10). In the case of **6a**, TsOH was added to the reaction mixture formed after the reaction of **6a** with MeONa in MeOH followed by refluxing for 25 min to give pyrrole **25a** in 89% yield. In all other cases, after completion of the reaction between **6b**, **23a,b** and MeONa in MeOH the solvent was evaporated, and the ring contraction reaction in the presence in TsOH was carried out in refluxing EtOH to produce pyrroles **25b–d**. The use of a one-pot procedure for **6a,b** increased the overall yield of the corresponding pyrroles.[27]



6a,**b**, **23a**,**b** **25a-d** (63-89%)

Scheme 10 Synthesis of 1-carbamoyl-1*H*-pyrroles **25a–d** from pyrimidines **6a,b**, **23a,b** using the ring expansion/ring contraction sequence.

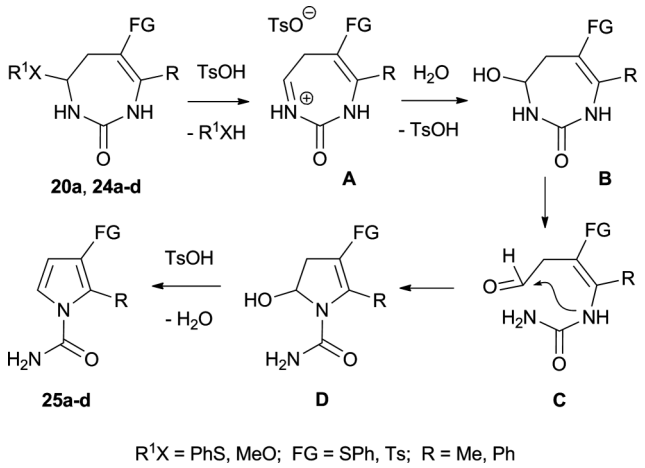
A plausible mechanism of transformation of diazepinones **20**, **24** into 1-carbamoylpyrroles **25** is outlined in Scheme 11.

The mechanism includes formation of acyliminium ions **A** as a result of acid-catalyzed elimination of MeOH followed by the addition of water, which affords 4-hydroxydiazepinones **B**. Ring opening of the latter with subsequent recyclization of the obtained ureas **C** leads to pyrrolines **D**, dehydration of which under the action of TsOH gives the final products. The participation of water in this process is in good agreement with experimental data (Table 3, entry 3 *vs.* entry 5).

Table 3 Acid-catalyzed ring contraction reaction of diazepinones **20a**, **24a–d** into 1-carbamoyl-1*H*-pyrroles **25a–d**[a]

Entry	Starting material	Solvent[b]	Equiv. of TsOH	Reaction time, min	Product(s)	Yield of **25**[d] (%)
1	**24a**	MeOH	0.10	30	**25a**	89
2	**20a**	EtOH	0.21	240	**25a**	84
3	**24b**	MeOH	0.10	180	**21b**+**24b**+**25b**[c]	—
4	**24b**	EtOH	0.05	10	**25b**	78
5	**24b**	MeOH–H_2O, 95 : 5	0.1	50	**25b**	78
6	**24c**	EtOH	0.1	15	**25c**	88
7	**24d**	EtOH	0.1	60	**25d**	96

[a] Reflux in alcohols in the presence of TsOH. [b] 99.5% MeOH and 95% EtOH were used. [c] In a ratio of 25 : 14 : 61, respectively. [d] Isolated yield.



Scheme 11 Transformation of **20a**, **24a–d** into 1-carbamoylpyrroles **25a–d**.

Conclusions

A six-step approach to 6-phenylthio-substituted 2,3,4,5-tetrahydro-1,3-1*H*-diazepin-2-ones based on the ring expansion reaction of 4-mesyloxymethyl-1,2,3,4-tetrahydropyrimidin-2-ones under the action of various nucleophiles was developed. Synthesis of pyrimidinones included the reaction of ureidoalkylation of sodium enolates of α-phenylthio-substituted ketones with readily available *N*-[(2-benzoyloxy-1-tosyl)ethyl]urea followed by heterocyclization–dehydration, debenzoylation and mesylation. A plausible mechanism of pyrimidine ring expansion involved formation of cyclopropane intermediates followed by spontaneous ring expansion and addition of a nucleophile to the formed acylimine. 3-Functionally substituted 1-carbamoyl-1*H*-pyrroles were synthesized from 4-methoxy- and 4-phenylthio-diazepinones under acidic conditions *via* ring contraction. A pathway for this transformation includes formation of acyliminium ions followed by addition of water, ring opening and closure to give the corresponding pyrroles. Effective one-pot synthesis of the latter from 4-mesyloxymethyl-pyrimidines was realized using the ring expansion/ring contraction sequence.

Experimental section

General

All used solvents were distilled before use. 95% EtOH was used unless otherwise indicated. The petroleum ether (PE) had a distillation range of 40–60 °C. Dry solvents (MeCN, THF, CH_2Cl_2, MeOH, EtOH, DMF) were obtained according to the standard procedures. Sodium hydride (NaH) (60% suspension in mineral oil) was thoroughly washed with dry pentane and dried in vacuum prior to use. All other reagents were purchased from commercial sources and used without additional purification. IR spectra (in Nujol) were recorded using a Bruker Vector 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 and proton-decoupled ^{13}C NMR spectra (solutions in DMSO-d_6) 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). In ^{13}C NMR spectra, the DMSO-d_6 signal (39.50 ppm) was used as a reference. 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. Thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} aluminum backed plates in chloroform–methanol (9 : 1, v/v) and chloroform–methanol (5 : 1, v/v) as solvent systems. Spots were visualized with iodine vapors or UV light. Column chromatography was performed with Merck silica gel 60 (0.04–0.063 mm). All yields refer to isolated, spectroscopically and TLC pure compounds. The color of analytically pure samples of all the obtained compounds is white except for compound **6b** (slightly yellow).

4-(Mesyloxymethyl)-6-phenyl-5-phenylthio-1,2,3,4-tetrahydropyrimidin-2-one (6b). To a cooled in an ice bath, stirred suspension of pyrimidine **14b** (3.500 g, 11.20 mmol) and DMAP (2.759 g, 22.58 mmol) in dry CH_2Cl_2 (25 mL) was added a solution of MsCl (1.933 g, 16.87 mmol) in dry CH_2Cl_2 (25 mL) over 5 min. The obtained suspension was stirred for 5 min, the ice bath was removed, stirring continued at room temperature for 2 h 20 min, and the solvent was removed in vacuum. The solid residue was triturated with ice-cold water (20 mL) and PE (15 mL), the suspension was cooled (0 °C), the precipitate was filtered, washed with ice-cold water, PE, cold ether, and dried to give crude **6b** (4.092 g) which was crystallized from 182 mL of MeCN (decolorizing with silica gel) to obtain **6b** (3.417 g, 78%) as a slightly yellow solid which was used in the ring expansion reactions; mp 170–170.5 °C (decomp., MeCN); found: C, 54.97; H, 4.86; N, 7.37. Calc. for $C_{18}H_{18}N_2O_4S_2$: C, 55.37; H, 4.65; N, 7.17; ν_{max}(Nujol)/cm^{-1} 3331br s, 3235br s, 3124sh, 3103br m (NH), 3052w, 3028w, 3012 w (CH_{arom}), 1711vs (amide I), 1632 m (C═C), 1580 m, 1497 m (CC_{arom}), 1338 s, 1170 s (SO_2), 741 s, 702 m (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 9.21 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.0 Hz, $N_{(1)}H$), 7.29–7.41 (8 H, m, ArH and $N_{(3)}H$), 7.12–7.23 (3 H, m, ArH), 4.39 (1 H, dd, $^2J_{CH(A),CH(B)}$ = 10.5, $^3J_{CH(A),4\text{-}H}$ = 4.5 Hz, H(A) in OCH_2), 4.16 (1 H, dd, $^2J_{CH(B),CH(A)}$ = 10.5, $^3J_{CH(B),4\text{-}H}$ = 2.6 Hz, H(B) in OCH_2), 3.94 (1 H, ddd, $^3J_{4\text{-}H,CH(A)}$ = 4.5, $^3J_{4\text{-}H,N(3)H}$ = 2.8, $^3J_{4\text{-}H,CH(B)}$ = 2.6 Hz, 4-H), 3.20 (3 H, s, CH_3SO_2); δ_C (75.48 MHz, DMSO-d_6) 152.8 (C-2), 148.5 (C-6), 136.3 (C), 134.0 (C), 129.4 (2CH), 129.2 (CH), 128.8 (2CH), 127.9 (2CH), 125.9 (2CH), 125.6 (CH), 92.6 (C-5), 71.4 (OCH_2), 54.6 (C-4), 36.9 (CH_3SO_2).

4-(Mesyloxymethyl)-6-methyl-5-phenylthio-1,2,3,4-tetrahydropyrimidin-2-one (6a). This compound was prepared according to the same procedure as described for **6b** from pyrimidine **14a** (2.803 g, 11.20 mmol), DMAP (1.936 g, 15.85 mmol) and MsCl (1.551 g, 13.54 mmol) in dry CH_2Cl_2 (50 mL) (rt, 2 h). The crude product (3.506 g) was crystallized from 12 mL of MeCN (decolorizing with silica gel) to give **6a** (2.501 g, 68%) as a white solid; mp 136.5–137 °C (decomp., MeCN); found: C, 47.57; H, 4.98; N, 8.67. Calc. for $C_{13}H_{16}N_2O_4S_2$: C, 47.55; H, 4.91; N, 8.53; ν_{max}(Nujol)/cm^{-1} 3413 m, 3377w, 3238br s, 3141br m (NH), 3077w, 3060w, 3020w, 3002 w (CH_{arom}), 1701 s, 1680 m (amide I), 1657 s (C═C), 1581 m (CC_{arom}), 1350 s, 1171 s (SO_2), 744 s, 692 m (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.97 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.1 Hz, $N_{(1)}H$), 7.30–7.37 (2 H, m, ArH), 7.24 (1 H, dd, $^3J_{N(3)H,4\text{-}H}$ = 2.7, $^4J_{N(3)H,N(1)H}$ = 2.1 Hz, $N_{(3)}H$), 7.14–7.23 (3 H, m, ArH), 4.18 (1 H, dd, $^2J_{CH(A),CH(B)}$ = 10.4, $^3J_{CH(A),4\text{-}H}$ = 4.6 Hz, H(A) in OCH_2), 4.06

(1 H, dd, $^{2}J_{CH(B),CH(A)}$ = 10.4, $^{3}J_{CH(B),4-H}$ = 2.7 Hz, H(B) in OCH_2), 3.91 (1 H, dddq, $^{3}J_{4-H,CH(A)}$ = 4.6, $^{3}J_{4-H,N(3)H}$ = 2.7, $^{3}J_{4-H,CH(B)}$ = 2.7, $^{5}J_{4-H,6-CH3}$ = 0.9 Hz, 4-H), 3.11 (3 H, s, CH_3SO_2), 1.97 (3 H, d, $^{5}J_{6-CH3,4-H}$ = 0.9 Hz, 6-CH_3); δ_C (75.48 MHz, DMSO-d_6) 152.6 (C-2), 146.1 (C-6), 136.3 (C), 129.3 (2CH), 125.7 (2CH), 125.5 (CH), 90.5 (C-5), 71.2 (OCH_2), 54.8 (C-4), 36.7 (CH_3SO_2), 16.9 (6-CH_3).

***N*-[(1-Benzoyloxy-4-oxo-4-phenyl-3-phenylthio)but-2-yl]urea (11b).** To a mixture of phenylthioacetophenone **10b** (2.328 g, 10.20 mmol) and NaH (0.244 g, 10.16 mmol) was added dry MeCN (14 mL), the mixture was stirred in an ice-cold bath for 11 min and to the resulting solution were added sulfone **9** (3.674 g, 10.14 mmol) and MeCN (5 mL). The suspension was stirred at room temperature for 8 h, and solvent was removed in vacuum. The oily residue was triturated with PE (3 × 15 mL), to the formed yellow solid was added satd. aqueous $NaHCO_3$ (8 mL) and PE (15 mL) and the obtained suspension was warmed on a water bath (40 °C) for 3 h, left overnight at room temperature, and cooled to 0 °C. The precipitate was filtered, washed with ice-cold water and PE. The solid obtained was dried in a vacuum desiccator (over P_2O_5) on the filter, cooled (–10 °C), washed with cold (–10 °C) ether (3 × 10 mL), and dried to give **11b** (3.600 g, 85%) as a slightly yellow solid with the ratio of diastereomers 78 : 22. After crystallization from ethyl acetate–hexane (4 : 1) compound **11b** was obtained as a white solid with a 88 : 12 diastereomeric ratio; mp 143.5–144.5 °C (EtOAc/hexane, 4 : 1, v/v); found: C, 66.31; H, 5.33; N, 6.69. Calc. for $C_{24}H_{22}N_2O_4S$: C, 66.34; H, 5.10; N, 6.45; ν_{max}(Nujol)/cm^{-1} 3448 s, 3326sh, 3300br s, 3195 m (NH), 3056 w (CH_{arom}), 1719 s (C═O in PhCOO), 1672 s (C═O in COPh), 1653 s (amide I), 1596w, 1582 m (CC_{arom}), 1551 s, 1533 s (amide II), 1274 s, 1119 s (C–O), 736 m, 717 s, 684 m (CH_{arom}); δ_H for the diastereomeric mixture (88 : 12) (300.13 MHz, DMSO-d_6) 7.84–7.98 (4 H, m, ArH), 7.58–7.69 (2 H, m, ArH), 7.35–7.55 (6 H, m, ArH), 7.23–7.55 (3 H, m, ArH), 6.40–6.47 (1 H, m, NH), 5.75 (0.24 H, s, NH_2 for the major isomer), 5.62 (1.76 H, s, NH_2 for the minor isomer), 5.20–5.28 (1 H, m, CH–S), 4.46–4.67 (2.64 H, m, OCH_2CH for the major isomer), 4.17–4.41 (0.36 H, m, OCH_2CH for the minor isomer); δ_C for the major diastereomer (75.48 MHz, DMSO-d_6) 194.8 (C═O in COPh), 165.5 (C═O in PhCOO), 157.9 ($NHCONH_2$), 135.8 (C), 133.5 (CH), 133.3 (CH), 132.6 (2CH), 132.3 (C), 129.5 (C), 129.3 (2CH), 129.2 (2CH), 128.7 (2CH), 128.5 (2CH), 128.4 (2CH), 128.3 (CH), 65.1 (OCH_2), 51.4 (CH–S), 49.6 (CH–N).

4-(Benzoyloxymethyl)-6-methyl-5-phenylthio-1,2,3,4-tetrahydropyrimidin-2-one (13a). To a mixture of phenylthioacetone **10a** (1.295 g, 7.79 mmol) and NaH (0.185 g, 7.71 mmol) was added dry MeCN (16 mL), the mixture was stirred in an ice-cold bath for 12 min and to the resulting solution were added sulfone **9** (2.771 g, 7.65 mmol) and MeCN (2 mL). The suspension was stirred at room temperature for 8 h, then TsOH·H_2O (1.948 g, 10.24 mmol) was added and the reaction mixture was refluxed under stirring for 2 h. At the beginning of the reflux the reaction mixture becomes very dense, which complicates stirring, thus the flask was shaken to keep the internal temperature of the mixture roughly the same throughout the entire volume. Without this procedure thermal decomposition of the mixture occurs at the bottom of the flask, which significantly reduces the purity and yield of the product. 20 min after the beginning of the reflux the suspension becomes fluid enough to be stirred normally. At the end of the reflux the reaction mixture becomes dark red. The solvent was removed in vacuum. The oily dark red residue was triturated with PE (3 × 15 mL), then satd. aqueous $NaHCO_3$ (8 mL) and PE (15 mL) were added, the mixture was warmed in a water bath (40 °C) for 3 h and left overnight at room temperature, then cooled to 0 °C, the oily substance was filtered using a glass filter, washed with ice-cold water and divided into small portions (for better drying). The filter with crude product was dried in a vacuum desiccator (over P_2O_5), cooled (–10 °C), the oily matter was triturated and washed with cold (–10 °C) ether until crystallization was complete, then ether was removed from powder by passing air through the filter and the product was washed with ice-cold water, and dried to give **13a** (2.382 g, 88%) as a pale brown solid. Recrystallization from EtOH afforded **13a** as a white solid; mp 200–201 °C (decomp., EtOH); found: C, 64.43; H, 5.26; N, 7.71. Calc. for $C_{19}H_{18}N_2O_3S$: C, 64.39; H, 5.12; N, 7.90; ν_{max}(Nujol)/cm^{-1} 3245br s, 3094br s (NH), 1725 s (C═O in PhCOO), 1699vs (amide I), 1663 m (C═C), 1603w, 1583 w (CC_{arom}), 1267 s, 1114 s (C–O), 744 m, 714 s, 690 m (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 9.08 (1 H, d, $^{4}J_{N(1)H,N(3)H}$ = 2.0 Hz, $N_{(1)}H$), 7.95–8.00 (2 H, m, ArH), 7.63–7.71 (1 H, m, ArH), 7.49–7.57 (2 H, m, ArH), 7.31 (1 H, dd, $^{3}J_{N(3)H,4-H}$ = 2.7, $^{4}J_{N(3)H,N(1)H}$ = 2.0 Hz, $N_{(3)}H$), 7.10–7.31 (5 H, m, ArH), 4.25 (1 H, dd, $^{2}J_{CH(A),CH(B)}$ = 11.2, $^{3}J_{CH(A),4-H}$ = 4.4 Hz, H(A) in OCH_2), 4.17 (1 H, dd, $^{2}J_{CH(B),CH(A)}$ = 11.2, $^{3}J_{CH(B),4-H}$ = 2.9 Hz, H(B) in OCH_2), 3.96 (1 H, dddq, $^{3}J_{4-H,CH(A)}$ = 4.4, $^{3}J_{4-H,CH(B)}$ = 2.9, $^{3}J_{4-H,N(3)H}$ = 2.7, $^{5}J_{4-H,6-CH3}$ = 0.8 Hz, 4-H), 1.96 (3 H, d, $^{5}J_{6-CH3,4-H}$ = 0.8 Hz, 6-CH_3); δ_C (75.48 MHz, DMSO-d_6) 165.7 (C═O in PhCOO), 153.2 (C-2), 145.8 (C-6), 136.7 (C), 133.4 (CH), 129.5 (C), 129.4 (2CH), 129.3 (2CH), 128.7 (2CH), 125.6 (2CH), 125.4 (CH), 91.5 (C-5), 66.6 (OCH_2), 54.9 (C-4), 16.9 (6-CH_3).

4-(Benzoyloxymethyl)-6-phenyl-5-phenylthio-1,2,3,4-tetrahydropyrimidin-2-one (13b). A solution of compound **11b** (5.115 g, 11.77 mmol) and TsOH·H_2O (1.147 g, 6.03 mmol) in dry MeCN (35 mL) was refluxed for 4 h under stirring and then the solvent was removed in vacuum. The solid residue was triturated with satd. aqueous $NaHCO_3$ (20 mL), PE (15 mL) was added, and the mixture was stirred at room temperature for 1 h for better grinding of the obtained precipitate, cooled to 0 °C, the precipitate was filtered, washed with ice-cold water, PE, and dried to give **13b** (4.803 g, 98%) as a pale yellow solid. Recrystallization from MeCN afforded **13b** as a white solid; mp 192–195 °C (MeCN); found: C, 69.24; H, 4.85; N, 6.61. Calc. for $C_{24}H_{20}N_2O_3S$: C, 69.21; H, 4.84; N, 6.73; ν_{max}(Nujol)/cm^{-1} 3365 s, 3195br s, 3088br s, 3066 s (NH), 1703 s (C═O in PhCOO), 1688vs (amide I), 1649 m (C═C), 1600w, 1580w, 1492 w (CC_{arom}), 1281 s, 1108 m (C–O), 742 m, 713 s, 699 s (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 9.22 (1 H, d, $^{4}J_{N(1)H,N(3)H}$ = 2.0 Hz, $N_{(1)}H$), 8.01–8.07 (2 H, m, ArH), 7.63–7.71 (1 H, m, ArH), 7.49–7.57 (2 H, m, ArH), 7.38 (1 H, dd, $^{3}J_{N(3)H,4-H}$ = 2.7, $^{4}J_{N(3)H,N(1)H}$ = 2.0 Hz, $N_{(3)}H$), 7.11–7.37 (10 H, m, ArH), 4.58 (1 H, dd, $^{2}J_{CH(A),CH(B)}$ = 11.2, $^{3}J_{CH(A),4-H}$ = 4.0 Hz, H(A) in OCH_2), 4.24 (1 H, dd, $^{2}J_{CH(B),CH(A)}$ = 11.2, $^{3}J_{CH(B),4-H}$ = 2.8 Hz, H(B) in OCH_2), 4.03 (1 H, ddd, $^{3}J_{4-H,CH(A)}$ = 4.0, $^{3}J_{4-H,CH(B)}$ = 2.8, $^{3}J_{4-H,N(3)H}$ = 2.7 Hz, 4-H); δ_C (75.48 MHz, DMSO-d_6) 165.7 (C═O in PhCOO), 153.2 (C-2), 147.9 (C-6), 136.5 (C), 134.0 (C), 133.4 (CH), 129.5 (C), 129.4 (2CH), 129.3 (2CH), 129.0 (CH), 128.7 (2CH), 128.6 (2CH), 127.8 (2CH), 125.9 (2CH), 125.5 (CH), 93.8 (C-5), 66.6 (OCH_2), 54.8 (C-4).

4-Hydroxymethyl-6-phenyl-5-phenylthio-1,2,3,4-tetrahydropyrimidin-2-one (14b). To a solution of KOH (1.158 g, 20.64 mmol)

in H_2O (10 mL) were added pyrimidine **13b** (4.803 g, 11.53 mmol) and EtOH (36 mL). The obtained suspension was stirred at room temperature for 2 h 50 min, cooled in an ice bath, neutralized with 15% aqueous HCl to pH 6, and the solvent was removed in vacuum. To the solid residue was added satd. aqueous $NaHCO_3$ (15 mL), the suspension was cooled to 0 °C, the precipitate was filtered, washed with ice-cold water, PE, cold (–10 °C) ether, and dried to give **14b** (3.078 g, 85%) as a yellow solid. Recrystallization from *n*BuOH afforded **14b** as a white solid; mp 241 °C (decomp., *n*BuOH); found: C, 65.42; H, 5.27; N, 8.95. Calc. $C_{17}H_{16}N_2O_2S$ (312.39): C, 65.36, H, 5.16; N, 8.97; ν_{max}(Nujol)/cm^{-1} 3378 m, 3340w, 3328w, 3288 m, 3213br s, 3086br s, 3075sh (NH, OH), 3031 w (CH_{arom}), 1670vs (amide I), 1658vs (C═C), 1601w, 1580w, 1495 w (CC_{arom}), 768 m, 742 s, 699 s (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.91 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.0 Hz, $N_{(1)}H$), 7.26–7.39 (7 H, m, ArH), 7.10–7.22 (3 H, m, ArH), 6.96 (1 H, dd, $^3J_{N(3)H,4\text{-}H}$ = 2.4, $^4J_{N(3)H,N(1)H}$ = 2.0, Hz, $N_{(3)}H$), 4.89 (1 H, t, $^3J_{OH,CH2}$ = 5.7 Hz, OH), 3.64 (1 H, ddd, $^3J_{4\text{-}H,CH(A)}$ = 5.7, $^3J_{4\text{-}H,CH(B)}$ = 2.9, $^3J_{4\text{-}H,N(3)H}$ = 2.4 Hz, 4-H), 3.58 (1 H, ddd, $^2J_{CH(A),CH(B)}$ = 11.0, $^3J_{CH(A),4\text{-}H}$ = 5.7, $^3J_{CH(A),OH}$ = 5.7 Hz, H(A) in OCH_2), 3.47 (1 H, ddd, $^2J_{CH(B),CH(A)}$ = 11.0, $^3J_{CH(B),OH}$ = 5.7, $^3J_{CH(B),4\text{-}H}$ = 2.9 Hz, H(B) in OCH_2); δ_C (75.48 MHz, DMSO-d_6) 153.3 (C-2), 147.1 (C-6), 136.9 (C), 134.3 (C), 129.2 (2CH), 128.9 (CH), 128.8 (2CH), 127.7 (2CH), 125.7 (2CH), 125.2 (CH), 94.7 (C-5), 63.6 (OCH_2), 57.6 (C-4).

4-Hydroxymethyl-6-methyl-5-phenylthio-1,2,3,4-tetrahydropyrimidin-2-one (14a). Compound **14a** (1.978 g, 70%) as a pale brown solid was prepared from pyrimidine **13a** (4.018 g, 11.34 mmol) and KOH (1.139 g, 20.30 mmol) in H_2O (10 mL) and EtOH (35 mL) (2 h 45 min, rt) as described for **14b**. Recrystallization from EtOH (decoloration of boiling solution with charcoal) afforded **14a** as a white solid; mp 212–214 °C (decomp., EtOH); found: C, 57.71; H, 5.70; N, 11.12. Calc. for $C_{12}H_{14}N_2O_2S$: C, 57.58, H; 5.64; N, 11.19; ν_{max}(Nujol)/cm^{-1} 3296br s, 3261 s, 3141 m, 3108 m (NH, OH), 1703vs, 1695vs, 1674 m (amide I), 1651 s (C═C), 1578 m (CC_{arom}), 748 s, 698 m (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.72 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.1 Hz, $N_{(1)}H$), 7.27–7.35 (2 H, m, ArH), 7.10–7.22 (3 H, m, ArH), 6.82 (1 H, dd, $^3J_{N(3)H,4\text{-}H}$ = 2.7, $^4J_{N(3)H,N(1)H}$ = 2.1 Hz, $N_{(3)}H$), 4.75 (1 H, t, $^3J_{OH,CH2}$ = 5.6 Hz, OH), 3.57 (1 H, m, 4-H), 3.31–3.49 (2 H, m, OCH_2), 1.93 (3 H, d, $^5J_{6\text{-}CH3,4\text{-}H}$ = 1.0 Hz, 6-CH_3); δ_C (75.48 MHz, DMSO-d_6) 153.1 (C-2), 144.6 (C-6), 137.1 (C), 129.2 (2CH), 125.4 (2CH), 125.1 (CH), 92.4 (C-5), 63.7 (OCH_2), 57.9 (C-4), 16.8 (6-CH_3).

4-Cyano-7-phenyl-6-phenylthio-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (15b). A suspension of pyrimidine **6b** (0.571 g, 1.46 mmol), finely powdered NaCN (0.107 g, 2.18 mmol) and 18-crown-6 (0.051 g, 0.19 mmol) in dry MeCN (45 mL) was refluxed under stirring for 4 h. The solvent was removed in vacuum, the obtained oily residue was triturated upon cooling with H_2O (5 mL) and PE (5 mL) until crystallization was complete. The resulting suspension was cooled to 0 °C, the precipitate was filtered, washed with ice-cold water, PE, dried, and the product was purified by column chromatography on silica gel 60 (15 g) eluting with PE/$CHCl_3$ (from 50 : 50 to 0 : 100) to give **15b** (0.296 g, 63%) as a white solid; mp 228–229 °C (decomp., MeCN); found: C, 66.92; H, 4.98; N, 13.22. Calc. for $C_{18}H_{15}N_3OS$: C, 67.27; H, 4.70; N, 13.07; ν_{max}(Nujol)/cm^{-1} 3235 s, 3220sh, 3081 s (NH), 3056 w (CH_{arom}), 2242 w (CN), 1688vs (amide I), 1626 m (C═C), 769 s, 749 s, 701 s (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.61 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.2 Hz, $N_{(1)}H$), 7.87 (1 H, ddd, $^3J_{N(3)H,4\text{-}H}$ = 6.6, $^4J_{N(3)H,N(1)H}$ = 2.2, $^4J_{N(3)H,5\text{-}H(B)}$ = 0.8 Hz, $N_{(3)}H$), 7.15–7.38 (10 H, m, ArH), 4.73 (1 H, ddd, $^3J_{4\text{-}H,N(3)H}$ = 6.6, $^3J_{4\text{-}H,5\text{-}H(B)}$ = 5.0, $^3J_{4\text{-}H,5\text{-}H(A)}$ = 3.3 Hz, 4-H), 3.02 (1 H, dd, $^2J_{5\text{-}H(A),5\text{-}H(B)}$ = 16.3, $^3J_{5\text{-}H(A),4\text{-}H}$ = 3.3 Hz, 5-H(A)), 2.71 (1 H, ddd, $^2J_{5\text{-}H(B),5\text{-}H(A)}$ = 16.3, $^3J_{5\text{-}H(B),4\text{-}H}$ = 5.0, $^4J_{5\text{-}H(B),N(3)H}$ = 0.8 Hz, 5-H(B)); δ_C (75.48 MHz, DMSO-d_6) 154.9 (C-2), 144.1 (C-7), 138.0 (C), 136.4 (C), 129.3 (2CH), 128.5 (CH), 128.3 (2CH), 128.0 (2CH), 126.5 (2CH), 125.5 (CH), 118.5 (CN), 104.6 (C-6), 43.0 (C-4), 37.7 (C-5).

4-Cyano-7-methyl-6-phenylthio-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (15a). This compound was prepared according to the same procedure as described for **15b** from pyrimidine **6a** (0.643 g, 1.96 mmol), NaCN (0.144 g, 2.94 mmol) and 18-crown-6 (0.050 g, 0.19 mmol) in dry MeCN (41 mL) (5 h, reflux). The crude product was purified by column chromatography on silica gel 60 (16 g) eluting with PE/$CHCl_3$ (from 33 : 67 to 0 : 100) to afford pure **15a** (0.281 g, 55%) as a white solid; mp 204.5–205.5 °C (EtOH); found: C, 60.17; H, 5.19; N, 16.32. Calc. for $C_{13}H_{13}N_3OS$: C, 60.21; H, 5.05; N, 16.20; ν_{max}(Nujol)/cm^{-1} 3376 s, 3245 s, 3144br s (NH), 3073 w (CH_{arom}), 2243 w (C≡N), 1690vs (amide I), 1634 s (C═C), 1580 m, 1508 w (CC_{arom}), 737 s, 692 m (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.68 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.2 Hz, $N_{(1)}H$), 7.83 (1 H, ddd, $^3J_{N(3)H,4\text{-}H}$ = 7.0, $^4J_{N(3)H,N(1)H}$ = 2.2, $^4J_{N(3)H,5\text{-}H(B)}$ = 0.8 Hz, $N_{(3)}H$), 7.27–7.35 (2H, m, ArH), 7.13–7.23 (3 H, m, ArH), 4.63 (1 H, ddd, $^3J_{4\text{-}H,N(3)H}$ = 7.0, $^3J_{4\text{-}H,5\text{-}H(A)}$ = 3.3, $^3J_{4\text{-}H,5\text{-}H(B)}$ = 4.8 Hz, 4-H), 2.90 (1 H, ddq, $^2J_{5\text{-}H(A),5\text{-}H(B)}$ = 16.7, $^3J_{5\text{-}H(A),4\text{-}H}$ = 3.3, $^5J_{5\text{-}H(A),7\text{-}CH3}$ = 1.7 Hz, 5-H(A)), 2.58 (1 H, dddq, $^2J_{5\text{-}H(B),5\text{-}H(A)}$ = 16.7, $^3J_{5\text{-}H(B),4\text{-}H}$ = 4.8, $^4J_{5\text{-}H(B),N(3)H}$ = 0.8 Hz, $^5J_{5\text{-}H(B),7\text{-}CH3}$ = 0.7 Hz, 5-H(B)), 2.14 (3 H, dd, $^5J_{7\text{-}CH3,5\text{-}H(A)}$ = 1.7, $^5J_{7\text{-}CH3,5\text{-}H(B)}$ = 0.7 Hz, 7-CH_3); δ_C (75.48 MHz, DMSO-d_6) 155.6 (C-2), 141.1 (C-7), 136.1 (C), 129.2 (2CH), 126.3 (2CH), 125.5 (CH), 118.6 (CN), 101.0 (C-6), 41.9 (C-4), 38.9 (C-5), 21.3 (7-CH_3).

4-[Di(ethoxycarbonyl)methyl]-7-phenyl-6-phenylthio-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (16b). To a cooled in an ice bath, stirred suspension of NaH (0.016 g, 0.67 mmol) in dry THF (1 mL) was added a solution of diethyl malonate (0.117 g, 0.73 mmol) in THF (1.5 mL) over 2 min, and the solution was stirred for 8 min, then pyrimidine **6b** (0.207 g, 0.53 mmol) and THF (2.5 mL) were added. The resulting suspension was stirred at room temperature for 5 h, the solvent was removed in vacuum, and the solid residue was triturated with PE (2 mL) and H_2O (2 mL) until crystallization was complete. The obtained suspension was cooled (0 °C), the precipitate was filtered, washed with ice-cold water, PE, and dried to give **16b** (0.222 g, 92%) as a white solid; mp 116.5–118 °C (EtOH); found: C, 63.42; H, 5.93; N, 6.18. Calc. for $C_{24}H_{26}N_2O_5S$: C, 63.42; H, 5.77; N, 6.16; ν_{max}(Nujol)/cm^{-1} 3413 s, 3340w, 3211 s, 3095sh, 3080 s (NH), 3032w, 3013 w (CH_{arom}), 1728vs (C═O), 1679vs (amide I), 1620 s (C═C), 1579 m, 1494 m (CC_{arom}), 1255 s, 1159 s, 1038 s (C–O), 744 s, 695 s (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.24 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.2 Hz, $N_{(1)}H$), 7.28–7.39 (7 H, m, ArH), 7.14–7.22 (3 H, m, ArH), 7.09 (1 H, dd, $^3J_{N(3)H,4\text{-}H}$ = 4.6, $^4J_{N(3)H,N(1)H}$ = 2.2 Hz, $N_{(3)}H$), 4.04–4.19 (2 H, m, OCH_2), 4.07 (2 H, q, $^3J_{CH2,CH3}$ = 7.1 Hz, OCH_2), 4.01 (1 H, dddd, $^3J_{4\text{-}H,CH}$ = 8.8, $^3J_{4\text{-}H,5\text{-}H(B)}$ = 7.4, $^3J_{4\text{-}H,N(3)H}$ = 4.6, $^3J_{4\text{-}H,5\text{-}H(A)}$ = 2.7 Hz, 4-H), 3.76 (1 H, d, $^3J_{CH,4\text{-}H}$ = 8.8 Hz, CH in $CH(COOEt)_2$), 2.77 (1 H, dd, $^2J_{5\text{-}H(B),5\text{-}H(A)}$ = 15.3, $^3J_{5\text{-}H(B),4\text{-}H}$ = 7.4 Hz, 5-H(B)), 2.66 (1 H, dd, $^2J_{5\text{-}H(A),5\text{-}H(B)}$ = 15.3, $^3J_{5\text{-}H(A),4\text{-}H}$ = 2.7 Hz, 5-H(A)), 1.16 (3 H, t, $^3J_{CH3,CH2}$ = 7.1 Hz, CH_3 in COOEt), 1.12 (3 H, t,

$^3J_{CH3,CH2}$ = 7.1 Hz, CH_3 in COOEt); δ_C (75.48 MHz, DMSO-d_6) 166.8 (C═O in COOEt), 166.7 (C═O in COOEt), 155.5 (C-2), 143.8 (C-7), 137.7 (C), 136.3 (C), 129.2 (2CH), 128.5 (3CH), 127.9 (2CH), 126.7 (2CH), 125.5 (CH), 105.8 (C-6), 61.4 (OCH_2), 61.2 (OCH_2), 55.5 (CH in $CH(COOEt)_2$), 52.0 (C-4), 37.0 (C-5), 13.7 (CH_3 in COOEt).

4-[Di(ethoxycarbonyl)methyl]-7-methyl-6-phenylthio-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (16a). Diazepinone **16a** (0.177 g, 90%) as a white solid was prepared from pyrimidine **6a** (0.165 g, 0.50 mmol), diethyl malonate (0.108 g, 0.67 mmol) and NaH (0.015 g, 0.63 mmol) in dry THF (6.5 mL) (rt, 5 h) as described for **16b**; mp 124–129.5 °C (EtOH); found: C, 58.33; H, 6.29; N, 7.25. Calc. for $C_{19}H_{24}N_2O_5S$: C, 58.15; H, 6.16; N, 7.14; ν_{max}(Nujol)/cm^{-1} 3346w, 3304 s, 3212br s, 3104sh, 3072 m (NH), 1725vs (C═O), 1682 s (amide I), 1649 s (C═C), 1579w, 1499 w (CC_{arom}), 1258vs, 1156 s, 1027 s (C–O), 751 s, 689 m (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.32 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.1 Hz, $N_{(1)}H$), 7.25–7.34 (2 H, m, ArH), 7.21 (1 H, dd, $^3J_{N(3)H,4-H}$ = 5.7, $^4J_{N(3)H,N(1)H}$ = 2.1, Hz, $N_{(3)}H$), 7.08–7.19 (3 H, m, ArH), 3.94–4.19 (4 H, m, two OCH_2), 3.86 (1 H, dddd, $^3J_{4-H,CH}$ = 9.9, $^3J_{4-H,5-H(B)}$ = 6.1, $^3J_{4-H,N(3)H}$ = 5.7, $^3J_{4-H,5-H(A)}$ = 2.7 Hz, 4-H), 3.63 (1 H, d, $^3J_{CH,4-H}$ = 9.9 Hz, CH in $CH(COOEt)_2$), 2.64 (1 H, ddq, $^2J_{5-H(A),5-H(B)}$ = 16.1, $^3J_{5-H(A),4-H}$ = 2.7, $^5J_{5-H(A),7-CH3}$ = 1.5 Hz, 5-H(A)), 2.55 (1 H, br dd, $^2J_{5-H(B),5-H(A)}$ = 16.1, $^3J_{5-H(B),4-H}$ = 6.1 Hz, 5-H(B)), 2.10 (3 H, br s, 7-CH_3), 1.17 (3 H, t, $^3J_{CH3,CH2}$ = 7.1 Hz, CH_3 in COOEt), 1.11 (3 H, t, $^3J_{CH3,CH2}$ = 7.1 Hz, CH_3 in COOEt); δ_C (75.48 MHz, DMSO-d_6): δ = 166.8 (C═O in COOEt), 166.5 (C═O in COOEt), 155.9 (C-2), 140.7 (C-7), 136.4 (C), 129.1 (2CH), 126.5 (2CH), 125.4 (CH), 101.1 (C-6), 61.3 (OCH_2), 61.2 (OCH_2), 55.0 (CH in $CH(COOEt)_2$), 50.2 (C-4), 38.6 (C-5), 20.9 (7-CH_3), 13.72 (CH_3 in COOEt), 13.69 (CH_3 in COOEt).

7-Phenyl-6-phenylthio-4-phthalimido-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (17b). A suspension of pyrimidine **6b** (0.520 g, 1.33 mmol) and potassium phthalimide (0.370 g, 2.00 mmol) in dry MeCN (12 mL) was refluxed under stirring for 35 min, the solvent was removed in vacuum, to the solid residue was added H_2O (5 mL), the suspension was cooled to 0 °C, the precipitate was filtered, washed with ice-cold water, PE, and dried to give **17b** (0.566 g, 96%) as a slightly yellow solid. Recrystallization from DMF/EtOH (1 : 2) afforded **17b** as a white solid; mp 229.5 °C (decomp., DMF/EtOH, 1 : 2, v/v); found: C, 67.89; H, 4.73; N, 9.64. Calc. for $C_{25}H_{19}N_3O_3S$: C, 68.01; H, 4.34; N 9.52; ν_{max}(Nujol)/cm^{-1} 3228br s, 3180w, 3127w, 3096sh, 3082 m, 3055 m (NH), 3024 w (CH_{arom}), 1776 m, 1724vs (amide I, phthalimide fragment), 1686vs (amide I), 1628 m (C═C), 1581 m, 1493 m (CC_{arom}), 738 s, 718 s, 694 s (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.58 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.0 Hz, $N_{(1)}H$), 7.79–7.89 (4 H, m, ArH of phthalimide fragment), 7.16–7.46 (11 H, m, ArH and $N_{(3)}H$), 5.47 (1 H, ddd, $^3J_{4-H,5-H(A)}$ = 10.9, $^3J_{4-H,5-H(B)}$ = 3.1, $^3J_{4-H,N(3)H}$ = 1.0 Hz, 4-H), 3.77 (1 H, dd, $^2J_{5-H(A),5-H(B)}$ = 13.7, $^3J_{5-H(A),4-H}$ = 10.9 Hz, 5-H(A)), 2.60 (1 H, ddd, $^2J_{5-H(B),5-H(A)}$ = 13.7, $^3J_{5-H(B),4-H}$ = 3.1, $^4J_{5-H(B),N(3)H}$ = 1.5 Hz, 5-H(B)); δ_C (75.48 MHz, DMSO-d_6) 167.0 (2C═O of phthalimide fragment), 154.8 (C-2), 145.0 (C-7), 136.3 (C), 135.9 (C), 134.4 (2CH of phthalimide fragment), 131.5 (2 C of phthalimide fragment), 129.4 (2CH), 129.0 (CH), 128.9 (2CH), 127.9 (2CH), 126.9 (2CH), 125.8 (CH), 123.0 (2CH of phthalimide fragment), 107.9 (C-6), 61.6 (C-4), 35.9 (C-5).

7-Methyl-6-phenylthio-4-phthalimido-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (17a). Diazepinone **17a** (0.570 g, 96%) as a slightly yellow solid was prepared from pyrimidine **6a** (0.515 g, 1.57 mmol) and potassium phthalimide (0.430 g, 2.32 mmol) in MeCN (14 mL) (1 h 40 min, reflux) as described for **17b**. Recrystallization from MeCN afforded **17a** as a white solid; mp 195.5–196.5 °C (decomp., MeCN); found: C, 63.10; H, 4.70; N, 11.00. Calc. for $C_{20}H_{17}N_3O_3S$: C, 63.31; H, 4.52; N, 11.07; ν_{max}(Nujol)/cm^{-1} 3230br s, 3099br s, 3071sh (NH), 1778 m, 1719vs (amide I, phthalimide fragment), 1678 s (amide I), 1638 s (C═C), 1580 m (CC_{arom}), 745 m, 718 s, 691 m (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.49 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.0 Hz, $N_{(1)}H$), 7.79–7.87 (4 H, m, ArH of phthalimide fragment), 7.25–7.32 (2 H, m, ArH), 7.24 (1 H, br ddd, $^4J_{N(3)H,N(1)H}$ = 2.0, $^3J_{N(3)H,4-H}$ = 1.3, $^4J_{N(3)H,5-H(B)}$ ~ 1.2 Hz, $N_{(3)}H$), 7.11–7.19 (3 H, m, ArH), 5.40 (1 H, ddd, $^3J_{4-H,5-H(A)}$ = 10.5, $^3J_{4-H,5-H(B)}$ = 2.7, $^3J_{4-H,N(3)H}$ = 1.3 Hz, 4-H), 3.57 (1 H, ddq, $^2J_{5-H(A),5-H(B)}$ = 14.3, $^3J_{5-H(A),4-H}$ = 10.5, $^5J_{5-H(A),7-CH3}$ = 1.2 Hz, 5-H(A)), 2.47–2.55 (1 H, m, 5-H(B)), 2.08 (3 H, br d, $^5J_{7-CH3,5-H(A)}$ = 1.2 Hz, 7-CH_3); δ_C (75.48 MHz, DMSO-d_6) 166.9 (2C═O of phthalimide fragment), 154.5 (C-2), 142.8 (C-7), 135.8 (C), 134.4 (2CH of phthalimide fragment), 131.5 (2 C of phthalimide fragment), 129.2 (2CH), 126.9 (2CH), 125.7 (CH), 123.0 (2CH of phthalimide fragment), 104.8 (C-6), 61.0 (C-4), 36.8 (C-5), 19.7 (7-CH_3).

7-Phenyl-6-phenylthio-4-succinimido-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (18b). A suspension of NaH (0.029 g, 1.21 mmol) and succinimide (0.120 g, 1.21 mmol) in dry THF (5.5 mL) was stirred at room temperature for 1 h, then pyrimidine **6b** (0.317 g, 0.81 mmol) and THF (4.5 mL) were added and the resulted suspension was refluxed under stirring for 4 h, the solvent was removed in vacuum, the solid residue was triturated with H_2O (3 mL) until crystallization was complete, the suspension was cooled (0 °C), the precipitate was filtered, washed with ice-cold water, PE, and dried to give **18b** (0.294 g, 92%) as a white solid; mp 231 °C (decomp., DMF/EtOH, 1 : 1, v/v); found: C, 63.93; H, 4.94; N, 10.54. Calc. for $C_{21}H_{19}N_3O_3S$: C, 64.11; H, 4.87; N, 10.68; ν_{max}(Nujol)/cm^{-1} 3248 s, 3144 m, 3124 m (NH), 3066w, 3053 w (CH_{arom}), 1772 m, 1705vs (amide I, succinimide fragment), 1694sh (amide I), 1645 m (C═C), 1580 m, 1494 m (CC_{arom}), 769 m, 741 m, 705 m (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.50 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.0 Hz, $N_{(1)}H$), 7.31–7.43 (7 H, m, ArH), 7.17–7.29 (3 H, m, ArH), 7.03 (1 H, br s, $N_{(3)}H$), 5.28 (1 H, ddd, $^3J_{4-H,5-H(A)}$ = 11.1, $^3J_{4-H,5-H(B)}$ = 3.0, $^3J_{4-H,N(3)H}$ = 0.8 Hz, 4-H), 3.74 (1 H, dd, $^2J_{5-H(A),5-H(B)}$ = 13.7, $^3J_{5-H(A),4-H}$ = 11.1 Hz, 5-H(A)), 2.51 (4 H, s, CH_2CH_2 of succinimide fragment), 2.33 (1 H, ddd, $^2J_{5-H(B),5-H(A)}$ = 13.7, $^3J_{5-H(B),4-H}$ = 3.0, $^4J_{5-H(B),N(3)H}$ = 1.5 Hz, 5-H(B)); δ_C (75.48 MHz, DMSO-d_6) 176.8 (2C═O of succinimide fragment), 154.9 (C-2), 144.8 (C-7), 136.3 (C), 136.0 (C), 129.5 (2CH), 129.0 (CH), 128.8 (2CH), 127.9 (2CH), 126.6 (2CH), 125.7 (CH), 107.7 (C-6), 61.5 (C-4), 35.0 (C-5), 27.9 (CH_2CH_2 of succinimide fragment).

7-Methyl-6-phenylthio-4-succinimido-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (18a). Diazepinone **18a** (0.248 g, 93%) as a white solid was prepared from pyrimidine **6a** (0.264 g, 0.80 mmol), succinimide (0.119 g, 1.20 mmol) and NaH (0.029 g, 1.21 mmol) in dry THF (4.8 mL) (3 h 45 min, reflux) as described for **18b**; mp 221.5–222 °C (decomp., EtOH/DMF, 18 : 5, v/v); found: C, 57.71; H, 5.16; N, 12.63. Calc. for $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17; N, 12.68; ν_{max}(Nujol)/cm^{-1} 3244 s, 3148w, 3101 m (NH), 3071 w (CH_{arom}), 1773 m, 1708vs (amide I, succinimide fragment), 1694 s

(amide I), 1651 s (C═C), 1582 m, 1499 m (CC_{arom}), 741 s, 700 m (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.42 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.0 Hz, $N_{(1)}H$), 7.28–7.36 (2 H, m, ArH), 7.13–7.21 (3 H, m, ArH), 7.01 (1 H, ddd, $^4J_{N(3)H,N(1)H}$ = 2.0, $^4J_{N(3)H,5\text{-}H(B)}$ = 1.6, $^3J_{N(3)H,4\text{-}H}$ = 1.0 Hz, $N_{(3)}H$), 5.20 (1 H, ddd, $^3J_{4\text{-}H,5\text{-}H(A)}$ = 10.7, $^3J_{4\text{-}H,5\text{-}H(B)}$ = 2.6, $^3J_{4\text{-}H,N(3)H}$ = 1.0 Hz, 4-H), 3.57 (1 H, ddq, $^2J_{5\text{-}H(A),5\text{-}H(B)}$ = 14.3, $^3J_{5\text{-}H(A),4\text{-}H}$ = 10.7, $^5J_{5\text{-}H(A),7\text{-}CH3}$ = 1.3 Hz, 5-H(A)), 2.48 (4 H, s, CH_2CH_2 of succinimide fragment), 2.24 (1 H, ddd, $^2J_{5\text{-}H(B),5\text{-}H(A)}$ = 14.3, $^3J_{5\text{-}H(B),4\text{-}H}$ = 2.6, $^4J_{5\text{-}H(B),N(3)H}$ = 1.6 Hz, 5-H(B)), 2.05 (3 H, d, $^5J_{7\text{-}CH3,5\text{-}H(A)}$ = 1.3 Hz, 7-CH_3); δ_C (75.48 MHz, DMSO-d_6) 176.7 (2C═O of succinimide fragment), 154.5 (C-2), 142.4 (C-7), 135.8 (C), 129.3 (2CH), 126.7 (2CH), 125.6 (CH), 104.6 (C-6), 60.8 (C-4), 36.0 (C-5), 27.9 (CH_2CH_2 of succinimide fragment), 19.7 (7-CH_3).

7-Phenyl-6-phenylthio-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (19b). A suspension of pyrimidine **6b** (0.589 g, 1.51 mmol) and finely powdered $NaBH_4$ (0.062 g, 1.64 mmol) in dry THF (11 mL) was refluxed under stirring for 4 h 10 min. The solvent was removed in vacuum, the oily residue was triturated upon cooling with satd. aqueous $NaHCO_3$ (2 mL) and PE (3 mL) until complete crystallization. The resulting suspension was cooled to 0 °C, the precipitate was filtered, washed with ice-cold water, PE, dried, and the product was purified by column chromatography on silica gel 60 (13 g) eluting with PE/$CHCl_3$ (from 67 : 33 to 0 : 100) to give **19b** (0.322 g, 72%) as a white solid; mp 163–164.5 °C (MeCN); found: C, 68.95; H, 5.66; N, 9.56. Calc. for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N 9.45; ν_{max}(Nujol)/cm^{-1} 3212sh, 3204 s, 3088sh, 3069 s (NH), 3021 w (CH_{arom}), 1689vs (amide I), 1627 s (C═C), 1597w, 1580 m (CC_{arom}), 748 m, 736 m, 698 s (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 7.78 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.3 Hz, $N_{(1)}H$), 7.23–7.37 (8 H, m, ArH and $N_{(3)}H$), 7.10–7.19 (3 H, m, ArH), 3.25–3.33 (2 H, m, 4-H), 2.50–2.56 (2 H, m, 5-H); δ_C (75.48 MHz, DMSO-d_6) 157.5 (C-2), 143.6 (C-7), 139.1 (C), 136.9 (C), 129.2 (2CH), 128.3 (2CH), 128.1 (CH), 127.8 (2CH), 126.4 (2CH), 125.1 (CH), 106.4 (C-6), 40.9 (C-4), 36.3 (C-5).

7-Methyl-6-phenylthio-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (19a). This compound was prepared according to the same procedure as described for **19b** from pyrimidine **6a** (0.664 g, 2.02 mmol) and $NaBH_4$ (0.084 g, 2.22 mmol) in dry THF (10 mL) (1 h 50 min, reflux). The crude product was purified by column chromatography on silica gel 60 (12 g) eluting with $CHCl_3$ to afford pure **19a** (0.315 g, 66%) as a white solid; mp 142–143.5 °C (MeCN); found: C, 61.52; H, 5.94; N, 12.02. Calc. for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96; ν_{max}(Nujol)/cm^{-1} 3360w, 3270 s, 3144 m, 3115sh (NH), 3078w, 3069w, 3059w, 3024w, 3016 w (CH_{arom}), 1699vs (amide I), 1647 s (C═C), 1583 m, 1507 m (CC_{arom}), 728 s, 686 s (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.05 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.3 Hz, $N_{(1)}H$), 7.26–7.34 (2 H, m, ArH), 7.22 (1 H, dt, $^3J_{N(3)H,4\text{-}H}$ = 4.9, $^4J_{N(3)H,N(1)H}$ = 2.3 Hz, $N_{(3)}H$), 7.08–7.16 (3 H, m, ArH), 3.14–3.20 (2 H, m, 4-H), 2.38–2.44 (2 H, m, 5-H), 2.08 (3 H, t, $^5J_{7\text{-}CH3,5\text{-}H}$ = 1.3 Hz, 7-CH_3); δ_C (75.48 MHz, DMSO-d_6) 158.1 (C-2), 140.5 (C-7), 136.9 (C), 129.2 (2CH), 125.9 (2CH), 125.0 (CH), 102.7 (C-6), 40.2 (C-4), 37.5 (C-5), 21.6 (7-CH_3).

7-Phenyl-4,6-di(phenylthio)-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (20b). To a cooled in an ice bath, stirred suspension of NaH (0.039 g, 1.63 mmol) in dry THF (1.5 mL) was added a solution of thiophenol (0.180 g, 1.63 mmol) in THF (2.5 mL), the resulting white suspension was stirred for 12 min and pyrimidine **6b** (0.530 g, 1.36 mmol) and THF (2 mL) were added. The suspension was refluxed under stirring for 1 min, the solvent was removed in vacuum, the oily residue was triturated with PE (3 × 5 mL), then H_2O (3 mL) and PE (2 mL) were added and the product was triturated under cooling until complete crystallization. The suspension was cooled (0 °C), the precipitate was filtered, washed with ice-cold water, PE, and dried to give **20b** (0.521 g, 95%) as a slightly yellow solid. Recrystallization from MeCN afforded **20b** as a white solid; mp 173.5–175 °C (decomp., MeCN); found: C, 68.12, H, 5.05, N, 6.94. Calc. for $C_{23}H_{20}N_2OS_2$: C, 68.29; H, 4.98; N, 6.92; ν_{max}(Nujol)/cm^{-1} 3213br s, 3074 s, 3056 m (NH), 3018 w (CH_{arom}), 1675vs (amide I), 1612 m (C═C), 1579 m, 1492 m (CC_{arom}), 742 s, 699 s (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.40 (1H, d, $^4J_{N(1)H,N(3)H}$ = 2.2 Hz, $N_{(1)}H$), 7.80 (1 H, dd, $^3J_{N(3)H,4\text{-}H}$ = 5.3, $^4J_{N(3)H,N(1)H}$ = 2.2 Hz, $N_{(3)}H$), 7.44–7.51 (2 H, m, ArH), 7.13–7.39 (13 H, m, ArH), 4.99 (1 H, ddd, $^3J_{4\text{-}H,5\text{-}H(B)}$ = 6.4, $^3J_{4\text{-}H,N(3)H}$ = 5.3, $^3J_{4\text{-}H,5\text{-}H(A)}$ = 3.0 Hz, 4-H), 3.04 (1 H, dd, $^2J_{5\text{-}H(A),5\text{-}H(B)}$ = 15.4, $^3J_{5\text{-}H(A),4\text{-}H}$ = 3.0 Hz, 5-H(A)), 2.83 (1 H, dd, $^2J_{5\text{-}H(B),5\text{-}H(A)}$ = 15.4, $^3J_{5\text{-}H(B),4\text{-}H}$ = 6.4 Hz, 5-H(B)); δ_C (75.48 MHz, DMSO-d_6) 154.9 (C-2), 143.8 (C-7), 138.0 (C), 136.7 (C), 133.6 (C), 131.9 (2CH), 129.2 (2CH), 129.0 (2CH), 128.5 (CH), 128.4 (2CH), 127.9 (2CH), 127.3 (CH), 126.8 (2CH), 125.5 (CH), 105.4 (C-6), 61.0 (C-4), 41.1 (C-5).

7-Methyl-4,6-di(phenylthio)-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (20a). Diazepinone **20a** (0.333 g, 93%) as a white solid was prepared from pyrimidine **6a** (0.345 g, 1.05 mmol), thiophenol (0.139 g, 1.26 mmol) and NaH (0.030 g, 1.25 mmol) in dry THF (9 mL) (2 min, reflux) as described for **20b**; mp 133.5–135 °C (decomp.); found: C, 63.20; H, 5.45; N, 7.93. Calc. for $C_{18}H_{18}N_2OS_2$: C, 63.13; H, 5.30; N, 8.18; ν_{max}(Nujol)/cm^{-1} 3215br s, 3056br s (NH), 1684 s (amide I), 1638 s (C═C), 1580 m (CC_{arom}), 738 s, 690 m (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.55 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.2 Hz, $N_{(1)}H$), 7.89 (1 H, dd, $^3J_{N(3)H,4\text{-}H}$ = 6.5, $^4J_{N(3)H,N(1)H}$ = 2.2 Hz, $N_{(3)}H$), 7.41–7.47 (2 H, m, ArH), 7.23–7.36 (5 H, m, ArH), 7.11–7.22 (3 H, m, ArH), 4.93 (1 H, ddd, $^3J_{4\text{-}H,N(3)H}$ = 6.5, $^3J_{4\text{-}H,5\text{-}H(B)}$ = 5.1, $^3J_{4\text{-}H,5\text{-}H(A)}$ = 2.9 Hz, 4-H), 3.04 (1 H, ddq, $^2J_{5\text{-}H(A),5\text{-}H(B)}$ = 15.9 Hz, $^3J_{5\text{-}H(A),4\text{-}H}$ = 2.9, $^5J_{5\text{-}H(A),7\text{-}CH3}$ = 1.7 Hz, 5-H(A)), 2.71 (1 H, dd, $^2J_{5\text{-}H(B),5\text{-}H(A)}$ = 15.9, $^3J_{5\text{-}H(B),4\text{-}H}$ = 5.1 Hz, 5-H(B)), 2.11 (3 H, d, $^5J_{7\text{-}CH3,5\text{-}H(A)}$ = 1.7 Hz, 7-CH_3); δ_C (75.48 MHz, DMSO-d_6) 155.4 (C-2), 141.0 (C-7), 136.7 (C), 134.2 (C), 131.5 (2CH), 129.1 (2CH), 129.0 (2CH), 127.0 (CH), 126.3 (2CH), 125.3 (CH), 100.9 (C-6), 59.7 (C-4), 42.4 (C-5), 21.1 (7-CH_3).

4-Methoxy-7-methyl-6-phenylthio-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (24a). To a solution of MeONa in MeOH formed after dissolution of Na (0.063 g, 2.74 mmol) in dry MeOH (10 mL) was added pyrimidine **6a** (0.365 g, 1.11 mmol) and the resulting reaction mixture was stirred at room temperature for 2 h. 25 min after the beginning of the reaction the solution formed and after an additional 25 min new solid precipitated. The suspension was cooled in an ice bath, neutralized by AcOH (0.100 mL, 1.75 mmol), the excess of AcOH was removed by addition of solid $NaHCO_3$ (0.050 g),[28] and the mixture was stirred in an ice bath for 5 min. Then the solvent was removed in vacuum (with the temperature of the bath not higher than 30 °C), the oily residue was triturated with H_2O (2 mL), satd. aqueous $NaHCO_3$ (1 mL) and PE (3 mL) until crystallization was complete, the obtained suspension was cooled (0 °C), the precipitate was filtered, washed with ice-cold water, PE, and dried to give **24a** (0.285 g, 97%) as an almost white

solid.[29] Recrystallization from MeOH/H_2O (2 : 1) afforded **24a** as a white solid; mp 54–56 °C (MeOH/H_2O, 2 : 1, v/v); found: C, 59.15; H, 6.18; N, 10.50. Calc. for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60; ν_{max}(Nujol)/cm^{-1} 3218br s, 3072br s (NH), 1688 s, 1678sh (amide I), 1639vs (C═C), 1580 m (CC_{arom}), 1079 s (C–O), 739 s, 691 m (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.41 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.1 Hz, $N_{(1)}H$), 7.83 (1 H, dd, $^3J_{N(3)H,4\text{-}H}$ = 5.6, $^4J_{N(3)H,N(1)H}$ = 2.1 Hz, $N_{(3)}H$), 7.25–7.32 (2 H, m, ArH), 7.09–7.20 (3 H, m, ArH), 4.32 (1 H, ddd, $^3J_{4\text{-}H,N(3)H}$ = 5.6, $^3J_{4\text{-}H,5\text{-}H(B)}$ = 5.2, $^3J_{4\text{-}H,5\text{-}H(A)}$ = 2.0 Hz, 4-H), 3.21 (3 H, s, 4-OCH_3), 2.69 (1 H, ddq, $^2J_{5\text{-}H(A),5\text{-}H(B)}$ = 15.5, $^3J_{5\text{-}H(A),4\text{-}H}$ = 2.0, $^5J_{5\text{-}H(A),7\text{-}CH3}$ = 1.6 Hz, 5-H(A)), 2.58 (1 H, dd, $^2J_{5\text{-}H(B),5\text{-}H(A)}$ = 15.5, $^3J_{5\text{-}H(B),4\text{-}H}$ = 5.2 Hz, 5-H(B)), 2.03 (3 H, d, $^5J_{7\text{-}CH3,5\text{-}Ha}$ = 1.6 Hz, 7-CH_3); δ_C (75.48 MHz, DMSO-d_6) 155.3 (C-2), 140.2 (C-7), 137.0 (C), 129.0 (2CH), 126.0 (2CH), 125.0 (CH), 100.8 (C-6), 81.8 (C-4), 54.2 (OCH_3), 40.2 (C-5), 20.6 (7-CH_3).

4-Methoxy-7-phenyl-6-phenylthio-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (24b). Diazepinone **24b** (0.648 g, 97%) as a white solid was prepared from pyrimidine **6b** (0.797 g, 2.04 mmol), Na (0.117 g, 5.09 mmol) and dry MeOH (17 mL) (4 h, rt) as described for **24a**; mp 162–163.5 °C (decomp., EtOH); found: C, 66.21; H, 5.68; N, 8.66. Calc. for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58; ν_{max}(Nujol)/cm^{-1} 3319 br w, 3231 s, 3095 s, 3080sh (NH), 3055 w (CH_{arom}), 1677vs (amide I), 1619 m (C═C), 1579 m, 1493 m (CC_{arom}), 1070vs (C–O), 769 m, 747 s, 699 s (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.33 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.2 Hz, $N_{(1)}H$), 7.72 (1 H, dd, $^3J_{N(3)H,4\text{-}H}$ = 4.7, $^4J_{N(3)H,N(1)H}$ = 2.2 Hz, $N_{(3)}H$), 7.26–7.37 (7 H, m, ArH), 7.14–7.25 (3 H, m, ArH), 4.43 (1 H, ddd, $^3J_{4\text{-}H,5\text{-}H(B)}$ = 5.7, $^3J_{4\text{-}H,N(3)H}$ = 4.7, $^3J_{4\text{-}H,5\text{-}H(A)}$ = 3.0 Hz, 4-H), 3.24 (3 H, s, 4-OCH_3), 2.75 (1 H, dd, $^2J_{5\text{-}H(A),5\text{-}H(B)}$ = 14.8, $^3J_{5\text{-}H(A),4\text{-}H}$ = 3.0 Hz, 5-H(A)), 2.71 (1 H, dd, $^2J_{5\text{-}H(B),5\text{-}H(A)}$ = 14.8, $^3J_{5\text{-}H(B),4\text{-}H}$ = 5.7 Hz, 5-H(B)); δ_C (75.48 MHz, DMSO-d_6) 155.1 (C-2), 143.3 (C-7), 137.5 (C), 137.1 (C), 129.2 (2CH), 128.6 (2CH), 128.5 (CH), 127.8 (2CH), 126.5 (2CH), 125.3 (CH), 105.3 (C-6), 83.8 (C-4), 54.2 (OCH_3), 38.8 (C-5).

4-Methoxy-7-methyl-6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (24c). Diazepinone **24c** (0.499 g, 95%) as a white solid was prepared from pyrimidine **23a** (0.636 g, 1.70 mmol), Na (0.097 g, 4.22 mmol) and dry MeOH (15.5 mL) (50 min, rt) as described for **24a**; mp 173 °C (decomp., EtOH) when the rate of heating was about 1 °C in 15 s (fast heating), mp 180.5 °C with decomposition without melting at 170–171 °C when the rate of heating was more than 1 °C in 15 s; found C, 54.22; H, 6.02; N, 9.05. Calc. for $C_{14}H_{18}N_2O_4S$: C, 54.18; H, 5.85; N, 9.03; ν_{max}(Nujol)/cm^{-1} 3297 s, 3228 s, 3093br s (NH), 1685vs (amide I), 1632vs (C═C), 1518 m (CC_{arom}), 1299 s, 1147 s (SO_2), 1076 s (C–O), 812 s (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.70 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.0 Hz, $N_{(1)}H$), 8.13 (1 H, dd, $^3J_{N(3)H,4\text{-}H}$ = 5.6, $^4J_{N(3)H,N(1)H}$ = 2.0, Hz, $N_{(3)}H$), 7.69–7.74 (2 H, m, ArH), 7.35–7.41 (2 H, m, ArH), 4.40 (1 H, ddd, $^3J_{4\text{-}H,5\text{-}H(B)}$ = 6.1, $^3J_{4\text{-}H,N(3)H}$ = 5.6, $^3J_{4\text{-}H,5\text{-}H(A)}$ = 1.4 Hz, 4-H), 3.26 (1 H, dd, $^2J_{5\text{-}H(B),5\text{-}H(A)}$ = 15.4, $^3J_{5\text{-}H(B),4\text{-}H}$ = 6.1 Hz, 5-H(B)), 3.17 (3 H, s, 4-OCH_3), 2.48 (1 H, ddq, $^2J_{5\text{-}H(A),5\text{-}H(B)}$ = 15.4, $^3J_{5\text{-}H(A),4\text{-}H}$ = 1.4, $^5J_{5\text{-}H(A),7\text{-}CH3}$ = 1.5 Hz, 5-H(A)), 2.38 (3 H, s, CH_3 in Ts), 2.04 (3 H, d, $^5J_{7\text{-}CH3,5\text{-}H(A)}$ = 1.5 Hz, 7-CH_3); δ_C (75.48 MHz, DMSO-d_6) 154.0 (C-2), 145.1 (C-7), 142.9 (C), 140.3 (C), 129.4 (2CH), 126.6 (2CH), 113.2 (C-6), 81.2 (C-4), 54.1 (OCH_3), 32.6 (C-5), 21.0 (CH_3 in Ts), 19.4 (7-CH_3).

4-Methoxy-7-phenyl-6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (24d). To a solution of MeONa in MeOH formed after dissolution of Na (0.155 g, 6.74 mmol) in dry MeOH (20 mL) was added pyrimidine **23b** (1.016 g, 2.70 mmol) and the resulted suspension was refluxed under stirring for 2 min. The obtained solution was cooled in an ice bath, neutralized by AcOH (0.236 mL, 4.12 mmol), to the formed suspension was added solid $NaHCO_3$ (0.080 g) to remove the access of AcOH, the mixture was stirred in an ice bath for 5 min. Then the solvent was removed in vacuum (the temperature of bath not higher than 30 °C), the oily residue was triturated with H_2O (5 mL), satd. aqueous $NaHCO_3$ (3 mL) and PE (10 mL) until complete crystallization, the obtained suspension was cooled (0 °C), the precipitate was filtered, washed with ice-cold water, PE, and dried to give **24d** (0.938 g, 93%) as a slightly yellow solid. Recrystallization from MeCN afforded **24d** as a white solid; mp 175 °C (decomp., MeCN); found: C, 61.23; H, 5.61; N, 7.56. Calc. for $C_{19}H_{20}N_2O_4S$: C, 61.27; H, 5.41; N, 7.52; ν_{max}(Nujol)/cm^{-1} 3225br s, 3088br s (NH), 1684vs (amide I), 1627 s (C═C), 1596 m, 1490 m (CC_{arom}), 1316vs, 1148 s (SO_2), 1084 s, 1069 s (C–O), 812 s, 768 m, 699 s (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 8.57 (1 H, d, $^4J_{N(1)H,N(3)H}$ = 2.0 Hz, $N_{(1)}H$), 8.04 (1 H, dd, $^3J_{N(3)H,4\text{-}H}$ = 4.8, $^4J_{N(3)H,N(1)H}$ = 2.0 Hz, $N_{(3)}H$), 7.12–7.37 (7 H, m, ArH), 6.94–7.04 (2 H, m, ArH), 4.42 (1 H, ddd, $^3J_{4\text{-}H,5\text{-}H(B)}$ = 6.7, $^3J_{4\text{-}H,N(3)H}$ = 4.8, $^3J_{4\text{-}H,5\text{-}H(A)}$ = 2.0 Hz, 4-H), 3.28 (1 H, dd, $^2J_{5\text{-}H(B),5\text{-}H(A)}$ = 15.0, $^3J_{5\text{-}H(B),4\text{-}H}$ = 6.7 Hz, 5-H(B)), 3.25 (3 H, s, 4-OCH_3), 2.69 (1 H, dd, $^2J_{5\text{-}H(A),5\text{-}H(B)}$ = 15.0, $^3J_{5\text{-}H(A),4\text{-}H}$ = 2.0 Hz, 5-H(A)), 2.32 (3 H, s, CH_3 in Ts); δ_C (75.48 MHz, DMSO-d_6) 153.6 (C-2), 147.1 (C-7), 142.6 (C), 139.4 (C), 134.7 (C), 129.8 (2CH), 129.1 (CH), 128.9 (2CH), 127.2 (2CH), 127.0 (2CH), 116.6 (C-6), 82.7 (C-4), 54.2 (OCH_3), 32.1 (C-5), 20.9 (CH_3 in Ts).

1-Carbamoyl-2-methyl-3-phenylthio-1*H*-pyrrole (25a).

Method A. A solution of diazepinone **24a** (0.213 g, 0.81 mmol) and TsOH·H_2O (0.015 g, 0.08 mmol) in MeOH (7 mL) was refluxed under stirring for 30 min, then the solvent was removed in vacuum, the oily residue was triturated with satd. aqueous $NaHCO_3$ (2 mL) and PE (2 mL) until crystallization was complete, the obtained suspension was cooled (0 °C), the precipitate was filtered, washed with ice-cold water, PE, and dried to give **25a** (0.166 g, 89%) as an almost white solid.

Method B. To a solution of MeONa in MeOH formed after dissolution of Na (0.049 g, 2.13 mmol) in dry MeOH (7 mL) was added pyrimidine **6a** (0.283 g, 0.86 mmol) and the reaction mixture was stirred at room temperature for 2.5 h, to a formed suspension was added TsOH·H_2O (0.292 g, 1.54 mmol) and the reaction mixture was refluxed under stirring for 25 min, the solvent was removed in vacuum, the oily residue was triturated with satd. aqueous $NaHCO_3$ (1 mL), H_2O (1 mL) and PE (5 mL) until complete crystallization, the suspension was cooled (0 °C), the precipitate was filtered, washed with ice-cold water, PE, and dried to give **25a** (0.177 g, 89%) as a slightly yellow solid. The analytically pure sample (white crystals) was obtained using column chromatography on silica gel 60 (5 g) eluting with PE/$CHCl_3$ (from 3 : 1 to 1 : 1) followed by crystallization from PE/$CHCl_3$ (~1 : 1, v/v); mp 109–110 °C; found: C, 61.93; H, 5.24; N, 11.91. Calc. for $C_{12}H_{12}N_2OS$: C, 62.04; H, 5.21; N, 12.06; ν_{max}(Nujol)/cm^{-1} 3360 s, 3325sh, 3238 m, 3196 s (NH), 3074w, 3057 w (CH_{arom}), 1739 m, 1688vs (amide I), 1634 m, 1617 m, 1580 m, 1498 m (CC_{arom}), 736 s, 688 m (CH_{arom}); δ_H (300.13 MHz,

DMSO-d_6) 7.65 (2 H, br s, NH_2), 7.35 (1 H, d, $^3J_{5\text{-H},4\text{-H}}$ = 3.4 Hz, 5-H), 7.21–7.28 (2 H, m, ArH), 7.06–7.13 (1 H, m, ArH), 6.98–7.03 (2 H, m, ArH), 6.24 (1 H, d, $^3J_{4\text{-H},5\text{-H}}$ = 3.4 Hz, 4-H), 2.42 (3 H, s, 2-CH_3); δ_C (75.48 MHz, DMSO-d_6) 152.1 (C═O), 138.5 (C-2), 135.6 (C), 129.0 (2CH), 125.4 (2CH), 124.9 (CH), 120.0 (C-5), 114.6 (C-4), 109.1 (C-3), 12.6 (2-CH_3).

Method C. Pyrrole **25a** (0.116 g, 84%) as an almost white solid was prepared by refluxing a solution of diazepinone **20a** (0.205 g, 0.60 mmol) in EtOH (3.2 mL) in the presence of TsOH·H_2O (0.024 g, 0.12 mmol) for 4 h as described in Method A.

1-Carbamoyl-2-phenyl-3-phenylthio-1*H*-pyrrole (25b).

Method A. A solution of diazepinone **24b** (0.108 g, 0.33 mmol) and TsOH·H_2O (0.003 g, 0.02 mmol) in EtOH (2 mL) was refluxed under stirring for 8 min, then the solvent was removed under vacuum, the oily residue was dissolved in $CHCl_3$ (5 mL), and the solution was washed with H_2O (3 × 2 mL) and brine (2 × 1 mL). The solvent was removed in vacuum and the residue was co-evaporated with absolute EtOH (2 mL), the residual oil was kept under high vacuum for 3 h to remove traces of solvent to give **25b** (0.076 g, 78%) as a slightly yellow oil.

Method B. To a solution of MeONa in MeOH formed after dissolution of Na (0.035 g, 1.52 mmol) in dry MeOH (7 mL) was added pyrimidine **6b** (0.238 g, 0.61 mmol) and the suspension was stirred at room temperature for 4 h, to a formed suspension was added TsOH·H_2O (0.206 g, 1.08 mmol), and the solvent was removed in vacuum. To the resulting solid residue was added EtOH (6 mL), the reaction mixture was refluxed under stirring for 5 min, the solvent was removed in vacuum, the oily residue was dissolved in $CHCl_3$ (15 mL), and the solution was washed with H_2O (3 × 5 mL) and brine (2 × 3 mL). The solvent was removed in vacuum, the residue was co-evaporated with absolute EtOH (3 × 3 mL), and the residual oil was kept under high vacuum for 3 h to give **25b** (0.134 g, 75%) as a slightly yellow oil. The white crystals of pyrrole **25b** were obtained after addition of ether (2 mL) to the oil, which first dissolved in ether and then the crystals precipitated. The suspension was cooled (–10 °C), the crystals were filtered as fast as possible through a previously cooled glass filter (the crystals are highly soluble in ether), washed with cold ether (1 mL), and dried to give 0.061 g of **25b** (from 0.134 g of the oil). The analytically pure sample was obtained using column chromatography on silica gel 60 eluting with $CHCl_3$/PE (1 : 3) followed by ether work-up as described above; mp 116.5–118 °C; found: C, 69.33, H, 4.67, N, 9.53. Calc. for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52; ν_{max}(Nujol)/cm^{-1} 3451 s, 3408 s, 3311br s, 3235 s, 3168br s, 3150w, 3117 w (NH), 3067w, 3040w, 3019 w (CH_{arom}), 1724 s, 1692vs (amide I), 1614w, 1591 m, 1581 m, 1500 w (CC_{arom}), 77 s, 737 s, 700 s (CH_{arom}); δ_H (300.13 MHz, DMSO-d_6) 7.65 (2 H, br s, NH_2), 7.40 (1 H, d, $^3J_{5\text{-H},4\text{-H}}$ = 3.2 Hz, 5-H), 7.21–7.37 (7 H, m, ArH), 7.01–7.13 (3 H, m, ArH), 6.34 (1 H, d, $^3J_{4\text{-H},5\text{-H}}$ = 3.2 Hz, 4-H); δ_C (75.48 MHz, DMSO-d_6) 151.5 (C═O), 138.8 (C-2), 136.9 (C), 131.3 (C), 129.5 (2CH), 129.0 (2CH), 127.5 (2CH), 127.4 (CH), 125.7 (2CH), 125.1 (CH), 122.4 (C-5), 114.8 (C-4), 110.8 (C-3).

1-Carbamoyl-2-phenyl-3-tosyl-1*H*-pyrrole (25d).

Method A. A solution of diazepinone **24d** (0.506 g, 1.36 mmol) and TsOH·H_2O (0.026 g, 0.14 mmol) in EtOH (10 mL) was refluxed under stirring for 1 h, then the solvent was removed in vacuum, the oily residue was triturated with satd. aqueous $NaHCO_3$ (5 mL) and PE (5 mL) until crystallization was complete, the suspension was cooled (0 °C), the precipitate was filtered, washed with ice-cold water, PE, and dried to give **25d** (0.444 g, 96%) as a slightly yellow solid.

Method B. To a solution of MeONa in MeOH formed after dissolution of Na (0.050 g, 2.17 mmol) in dry MeOH (8 mL) was added pyrimidine **23b** (0.330 g, 0.88 mmol) and the resulted suspension was refluxed under stirring for 2 min, the formed solution was cooled, TsOH·H_2O (0.296 g, 1.56 mmol) was added and the solvent was removed in vacuum. To the resulting solid residue EtOH (10 mL) was added, the reaction mixture was refluxed under stirring for 30 min, the solvent was removed in vacuum, the obtained oily residue was triturated with satd. aqueous $NaHCO_3$ (3 mL) and PE (5 mL) until crystallization was complete, the obtained suspension was cooled (0 °C), the precipitate was filtered, washed with ice-cold water, PE, and dried to give **25d** (0.249 g, 83%) as a slightly yellow solid. Recrystallization from MeCN afforded **25d** as a white solid; mp 201–202 °C (decomp., MeCN); found C, 63.45; H, 4.87; N, 8.26. Calc. for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23; ν_{max}(Nujol)/cm^{-1} 3409 s, 3365 m, 3306 s, 3218 s, 3168w, 3137 w (NH), 3060 w (CH_{arom}), 1737 s, 1713vs (amide I), 1631 s, 1597 m, 1506 w (CC_{arom}), 1299 s, 1146vs (SO_2), 815 m, 775 s, 741 m, 713 m, 692 s (CH_{arom}); δ_H (300 MHz, DMSO-d_6) 7.75 (2 H, br s, NH_2), 7.28–7.44 (5 H, m, ArH), 7.31 (1 H, d, $^3J_{5\text{-H},4\text{-H}}$ = 3.3 Hz, 5-H), 7.13–7.25 (4 H, m, ArH), 6.68 (1 H, d, $^3J_{4\text{-H},5\text{-H}}$ = 3.3 Hz, 4-H), 2.31 (3 H, s, CH_3); δ_C (75.48 MHz, DMSO-d_6) 150.7 (C═O), 143.3 (C), 139.7 (C), 134.4 (C-2), 130.2 (2CH), 129.6 (C), 129.4 (2CH), 128.5 (CH), 127.4 (2CH), 126.4 (2CH), 124.9 (C-3), 121.2 (C-5), 109.5 (C-4), 20.9 (CH_3).

1-Carbamoyl-2-methyl-3-tosyl-1*H*-pyrrole (25c).

Method A. Pyrrole **25c** (0.265 g, 88%) as an almost white solid was prepared by refluxing a solution of diazepinone **24c** (0.336 g, 1.08 mmol) in EtOH (6 mL) in the presence of TsOH·H_2O (0.021 g, 0.11 mmol) for 15 min as described for **25d** according to Method A.

Method B. To a solution of MeONa in MeOH formed after dissolution of Na (0.049 g, 2.13 mmol) in dry MeOH (8 mL) was added pyrimidine **23a** (0.322 g, 0.86 mmol) and the resulted suspension was stirred at room temperature for 46 min, to a formed suspension was added TsOH·H_2O (0.293 g, 1.54 mmol) and the solvent was removed in vacuum. To the resulting solid residue was added EtOH (7 mL), the reaction mixture was refluxed under stirring for 15 min, the solvent was removed in vacuum, the obtained oily residue was triturated with satd. aqueous $NaHCO_3$ (3 mL) and PE (5 mL) until crystallization was complete, the obtained suspension was cooled (0 °C), the precipitate was filtered, washed with ice-cold water, PE, and dried to give **25c** (0.149 g, 63%) as a slightly yellow solid. Recrystallization from EtOH afforded **25c** as a white solid; mp 198.5–200 °C (decomp., EtOH); found C, 55.85; H, 5.32; N, 9.78. Calc. for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N 10.07; ν_{max}(Nujol)/cm^{-1} 3447 s, 3352w, 3259 s, 3201br s, 3145 m, 3125 w (NH), 1739vs (amide I), 1627 s, 1595w, 1509 w (CC_{arom}), 1312 s, 1144 s (SO_2), 809 m, 729 s, 709 s, 697 s (CH_{arom}); δ_H (300 MHz, DMSO-d_6) 7.85 (2 H, br s, NH_2), 7.71–7.77 (2 H, m, ArH), 7.36–7.42 (2 H, m, ArH), 7.20 (1 H, d, $^3J_{5\text{-H},4\text{-H}}$ = 3.5 Hz, 5-H), 6.49 (1 H, d, $^3J_{4\text{-H},5\text{-H}}$ = 3.5 Hz, 4-H), 2.56 (3 H, s, 2-CH_3), 2.36 (3 H, s, CH_3 in Ts); δ_C (75.48 MHz, DMSO-d_6) 151.5 (C═O),

143.4 (C), 140.3 (C), 133.6 (C-2), 129.9 (2CH), 126.3 (2CH), 123.3 (C-3), 120.2 (C-5), 109.0 (C-4), 21.0 (CH_3 in Ts), 12.0 (2-CH_3).

Acknowledgements

This research was supported by the Presidential grant for young scientists no. MK-4400.2011.3.

Notes and references

1 For reviews on 1,3-diazepines, see: (*a*) W. M. De Borggraeve and A. M. Van den Bogaert, "1,3-Diazepines" in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Oxford, 2008, vol. 13, pp. 161-181; (*b*) R. J. Herr, "Seven-Membered Hetarenes with Two or More Heteroatoms" in *Science of Synthesis*, ed. S. M. Weinreb, Georg Thieme Verlag, Stuttgart, 2004, vol. 17, pp. 929-972; (*c*) J. T. Sharp, "Seven-membered ring compounds containing nitrogen in the ring" in *Rodd's Chemistry of Carbon Compounds*, ed. M. Sainsbury, Elsevier, Amsterdam, 1999, Second Supplements to the 2nd Edition, vol. IV, part K, pp. 153-232; (*d*) G. V. Boyd, "Aromatic 7-ring systems with two or more heteroatoms" in *Houben–Weyl: Methods of Organic Chemistry*, ed. E. Schumann, Georg Thieme Verlag, Stuttgart, 1997, vol. E9d, pp. 299-508; (*e*) J. T. Sharp, "Seven-membered Rings with Two or More Heteroatoms" in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, 1997, vol. 7, Elsevier, CD-ROM version, pp. 593-651; (*f*) D. J. Le Count, "1,3-Diazepines" in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, 1996, vol. 9, Elsevier, Oxford, pp. 139-150; (*g*) F. D. Popp, A. C. Noble, "The Chemistry of Diazepines" in *Adv. Heterocycl. Chem.*, ed. A. R. Katritzky and A. J. Boulton, 1967, vol. 8, Academic Press, New York and London, pp. 21-82.

2 For recent examples on tetrahydro-1*H*-1,3-diazepin-2-ones synthesis, see: (*a*) A. Okano, S. Oishi, N. Fujii, H. Ohno and T. Tanaka, *J. Org. Chem.*, 2010, **75**, 3396–3400; (*b*) S. Belyakov, B. Duvall, D. Ferraris, G. Hamilton and M. Vaal, *WO Pat.*, WO2010/118006, 2010 [*Chem. Abstr.* 2010, **153**, 522238]; (*c*) O. R. Ludek, G. K. Schroeder, C. Liao, P. L. Russ, R. Wolfenden and V. E. Marquez, *J. Org. Chem.*, 2009, **74**, 6212–6223; (*d*) J. F. W. Keanna, P. Ordentlich and B. Goodenow, *WO Pat.*, WO2009/49018, 2009 [*Chem. Abstr.* 2009, **150**, 423234]; (*e*) K. Zhang, P. R. Chopade and J. Louie, *Tetrahedron Lett.*, 2008, **49**, 4306–4309; (*f*) A. Reisinger, R. Koch, P. V. Bernhardt and C. Wentrup, *Org. Biomol. Chem.*, 2004, **2**, 1227–1238; (*g*) I. M. Bell and C. A. Stump, *WO Pat.*, WO2006/29153, 2006 [*Chem. Abstr.* 2006, **144**, 292784]; (*h*) I. M. Bell, C. R. Theberge, T. M. Williams, C. B. Zartman, X. Zhang and S. N. Gallicchio, *WO Pat.*, WO2004/83187, 2004 [*Chem. Abstr.* 2004, **141**, 314326]; (*i*) M. D. McReynolds, K. T. Sprott and P. R. Hanson, *Org. Lett.*, 2002, **4**, 4673–4676.

3 J. J. Baldwin, D. E. McClure and D. A. Claremon, *US Pat.* 4677102, 1987 [*Chem. Abstr.* 1988, **109**, 54794].

4 (*a*) G. Cristalli, R. Volpini, S. Vittori, E. Camaioni, G. Rafaiani, S. Potenza and A. Vita, *Nucleosides Nucleotides*, 1996, **15**, 1567–1580; (*b*) V. E. Marquez, K. V. B. Rao, J. V. Silverton and J. A. Kelley, *J. Org. Chem.*, 1984, **49**, 912–919; (*c*) P. S. Liu, V. E. Marquez, J. S. Driscoll and R. W. Fuller, *J. Med. Chem.*, 1981, **24**, 662–666; (*d*) P. S. Liu, V. E. Marquez, J. A. Kelley and J. S. Driscoll, *J. Org. Chem.*, 1980, **45**, 5225–5227.

5 S. F. Martin, B. C. Follows, P. J. Hergenrother and C. L. Franklin, *J. Org. Chem.*, 2000, **65**, 4509–4514.

6 (*a*) J. Ashby and D. J. Griffiths, *J. Chem. Soc., Chem. Commun.*, 1974, 607–608; (*b*) J. Ashby and D. J. Griffiths, *J. Chem. Soc., Perkin Trans. 1*, 1975, 657–662; (*c*) E. Bullock, R. A. Garter, R. Cochrane, B. Gregory and D. C. Shields, *Can. J. Chem.*, 1977, **55**, 895–905; (*d*) D. A. Claremon and S. A. Rosenthal, *Synthesis*, 1986, 664–665.

7 For reviews, see: (*a*) C. O. Kappe, *Tetrahedron*, 1993, **49**, 6937–6963; (*b*) C. O. Kappe, *Acc. Chem. Res.*, 2000, **33**, 879–888; (*c*) M. A. Kolosov, V. D. Orlov, D. A. Beloborodov and V. V. Dotsenko, *Mol. Diversity*, 2009, **13**, 5–25.

8 For some recent examples, see: (*a*) P. M. Kumar, K. S. Kumar, S. R. Poreddy, P. K. Mohakhud, K. Mukkanti and M. Pal, *Tetrahedron Lett.*, 2011, **52**, 1187–1191; (*b*) G. B. D. Rao, B. N. Acharya, S. K. Verma and M. P. Kaushik, *Tetrahedron Lett.*, 2011, **52**, 809–812; (*c*) K. K. Pasunooti, H. Chai, C. N. Jensen, B. K. Gorityala, S. Wang and X.-W. Liu, *Tetrahedron Lett.*, 2011, **52**, 80–84; (*d*) V. F. Sedova and O. P. Shkurko, *Russ. J. Org. Chem.*, 2010, **46**, 1695–1701; (*e*) C. Mukhopadhyay and A. Datta, *J. Heterocycl. Chem.*, 2010, **47**, 136–146.

9 (*a*) A. Dondoni, A. Massi, S. Sabbatini and V. Bertolasi, *J. Org. Chem.*, 2002, **67**, 6979–6994; (*b*) M. V. Fernandez, F. J. L. Herrera and T. L. Cobos, *Heterocycles*, 1988, **27**, 2133–2140; (*c*) M. V. Fernandez, F. J. L. Herrera and T. L. Cobos, *Heterocycles*, 1986, **24**, 679–686; (*d*) F. J. L. Aparicio and F. J. L. Herrera, *Carbohydr. Res.*, 1979, **69**, 243–246.

10 (*a*) A. D. Shutalev and V. A. Kuksa, *Chem. Heterocycl. Compd.*, 1995, **31**, 86–91; (*b*) A. D. Shutalev and V. A. Kuksa, *Chem. Heterocycl. Compd.*, 1997, **33**, 91–95; (*c*) A. D. Shutalev, *Chem. Heterocycl. Compd.*, 1997, **33**, 1469–1470; (*d*) A. D. Shutalev, E. A. Kishko, N. V. Sivova and A. Yu. Kuznetsov, *Molecules*, 1998, **3**, 100–106; (*e*) A. A. Fesenko and A. D. Shutalev, *Tetrahedron Lett.*, 2007, **48**, 8420–8423; (*f*) A. A. Fesenko, D. A. Cheshkov and A. D. Shutalev, *Mendeleev Commun.*, 2008, **18**, 51–53; (*g*) A. A. Fesenko, P. A. Solovyev and A. D. Shutalev, *Tetrahedron*, 2010, **66**, 940–946; (*h*) A. A. Fesenko and A. D. Shutalev, *Tetrahedron*, 2010, **66**, 7219–7226; (*i*) A. D. Shutalev, E. V. Savinkina, D. V. Albov, I. A. Zamilatskov and E. A. Buravlev, *Struct. Chem.*, 2011, **22**, 849–855.

11 (*a*) A. A. Fesenko, M. L. Tullberg and A. D. Shutalev, *Tetrahedron*, 2009, **65**, 2344–2350; (*b*) A. A. Fesenko and A. D. Shutalev, *Tetrahedron*, 2011, **67**, 6876–6882.

12 (*a*) U. Groth, L. Richter and U. Schöllkopf, *Liebigs Ann. Chem.*, 1992, 199–202; (*b*) U. Schöllkopf and J. Mittendorf, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 613–614; (*c*) B. Gregory, E. Bullock and T.-S. Chen, *Can. J. Chem.*, 1985, **63**, 843–848; (*d*) D. A. Claremon, D. E. McClure, J. P. Springer and J. J. Baldwin, *J. Org. Chem.*, 1984, **49**, 3871–3874; (*e*) S. H. Kim and A. R. Martin, *J. Heterocycl. Chem.*, 1978, **15**, 1507–1508; (*f*) E. Bullock, B. Gregory and M. T. Thomas, *Can. J. Chem.*, 1977, **55**, 693–699; (*g*) H. P. M. Thiellier, G. J. Koomen and U. K. Pandit, *Tetrahedron*, 1977, **33**, 2609–2612; (*h*) H. P. M. Thiellier, G.-J. Koomen and U. K. Pandit, *Heterocycles*, 1976, **5**, 19–24; (*i*) H. P. M. Thiellier, G.-J. Koomen and U. K. Pandit, *Heterocycles*, 1975, **3**, 707–712; (*j*) G. B. Gill, D. J. Harper and A. W. Johnson, *J. Chem. Soc. C*, 1968, 1675–1683; (*k*) J. Ashby, L. A. Cort and J. A. Elvidge, *J. Chem. Soc. C*, 1968, 2311–2317; (*l*) R. F. Childs and A. W. Johnson, *J. Chem. Soc. C*, 1966, 1950–1955; (*m*) M. Anderson and A. W. Johnson, *J. Chem. Soc.*, 1965, 2411–2422; (*n*) P. J. Brignell, U. Eisner and H. Williams, *J. Chem. Soc.*, 1965, 4226–4231; (*o*) P. J. Brignell, E. Bullock, U. Eisner, B. Gregory, A. W. Johnson and H. Williams, *J. Chem. Soc.*, 1963, 4819–4827.

13 Our practical experience shows that both the yield and purity of sulfone **9** strongly depend on purity of starting materials, especially 2-benzoyloxyethanal **8**. The latter was prepared in three steps which included bromination of commercially available vinyl acetate in MeOH, subsequent treatment of the obtained dimethylacetal of 2-bromoethanal with PhCOONa in dry DMF followed by hydrolysis of dimethylacetal of 2-benzoyloxyethanal in 80% HCOOH. Detailed, procedure of 2-benzoyloxyethanal synthesis is described in the ESI† for this article.

14 Taking into consideration the experimental data obtained herein, greater excess of reagents required for mesylation of 4-hydroxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones (pyrimidine/MsCl/DMAP at the ratio of 1 : 2 : 3)[11] compared with 5-phenylthio-analogues can be explained by steric factors.

15 Decrease in the mesylation rate for **14b** compared with **14a** can be explained by low solubility of **14b** in CH_2Cl_2.

16 (*a*) V. E. Zavodnik, A. D. Shutalev, G. V. Gurskaya, A. I. Stash and V. G. Tsirelson, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2005, **61**, 365–367; (*b*) G. V. Gurskaya, V. E. Zavodnik and A. D. Shutalev, *Crystallogr. Rep.*, 2003, **48**, 92–97; (*c*) G. V. Gurskaya, V. E. Zavodnik and A. D. Shutalev, *Crystallogr. Rep.*, 2003, **48**, 416–421; (*d*) C. O. Kappe, W. M. F. Fabian and M. A. Semones, *Tetrahedron*, 1997, **53**, 2803–2816.

17 In contrast to 5-tosyl-substituted analogues[11] reaction of **6a,b** with NaCN in MeCN in the presence of 18-crown-6 did not proceed at room temperature (according to TLC).

18 A. A. Fesenko, L. A. Trafimova, D. A. Cheshkov and A. D. Shutalev, *Tetrahedron Lett.*, 2010, **51**, 5056–5059.

19 Compounds **21a,b** are representatives of monocyclic 2,3-dihydro-1*H*-1,3-diazepin-2-ones which remain practically unknown with only rare

examples described in the literature.[2f,30] Preparative synthesis of these heterocycles will be the subject of our forthcoming communications.
20 A. D. Shutalev, A. A. Fesenko, D. A. Cheshkov and D. V. Goliguzov, *Tetrahedron Lett.*, 2008, **49**, 4099–4101.
21 According to *ab initio* calculations (B3LYP/6-31+G(d,p))[22] performed for 4-mesyloxymethyl-1,2,3,4-tetrahydropyrimidin-2-one as a model compound, the anion resulted from $N_{(1)}H$ deprotonation in the gas phase is significantly more stable (10.3 kcal mol^{-1}) than the anion obtained after $N_{(3)}H$ deprotonation.
22 The ab initio calculations were carried out using the Gaussian 09 program: M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09, Revision A.02*, Gaussian, Inc., Wallingford CT, 2009.
23 According to *ab initio* calculations, the anion resulted from NH deprotonation of 2,4-diazabicyclo[4.1.0]hept-4-en-3-one is extremely unstable. This anion undergoes ring expansion to give *N*-anion of 1,5-dihydro-2*H*-1,3-diazepin-2-one without energy barrier in the gas phase or with very low activation barrier (0.12 kcal mol^{-1}) in MeCN. For, comparison, calculated activation barrier of electrocyclic opening of cyclopropane ring in 2,4-diazabicyclo[4.1.0]hept-4-en-3-one is 11.25 kcal mol^{-1} in the gas phase and 8.85 kcal mol^{-1} in MeCN.
24 Structure of *N*-anion of dihydrodiazepinone **21b** was confirmed by its ^{1}H NMR spectrum showing two doublets at 6.13 and 5.60 ppm due to the 7-H and 6-H protons with vicinal coupling constant 7.9 Hz. In addition, proton signals of 4-Ph group were considerably upfield shifted (6.72–6.99 ppm) compared with aromatic proton signals of dihydrodiazepinone **21b** (7.08–7.42 ppm).
25 The noticeable ^{1}H NMR characteristic of the bicyclic intermediate, 5-phenyl-6-(phenylthio)-2,4-diazabicyclo[4.1.0]hept-4-en-3-one, is a doublet of doublets at 5.53 ppm (J = 11.2 and 2.8 Hz) due to the 1-H proton.
26 The noticeable ^{1}H NMR characteristic of the bicyclic intermediate, 5-methyl-6-(phenylthio)-2,4-diazabicyclo[4.1.0]hept-4-en-3-one, is a doublet of doublets at 5.34 ppm (J = 10.5 and 2.5 Hz) due to the 1-H proton.
27 Decrease in the yield of both tosyl-substituted pyrroles (especially **25c**) is explained by partial loss of **25c,d** during work-up due to their moderate solubility in the solutions formed after addition of satd. $NaHCO_3$. Addition of water to these solutions did not cause additional precipitation of the products.
28 The removal of traces of AcOH by $NaHCO_3$ is especially important for preparation of diazepinone **24a** because it has a very strong tendency to ring contraction in the presence of acids. Neutralization of the reaction mixture with conc. HCl (with small excess towards the calculated amount) immediately led to formation of pyrrole **25a**.
29 Any contact of methoxy-diazepinone **24a** with EtOH (during work-up of the reaction mixture or when we attempted to crystallize it from $EtOH/H_2O$) led to formation of some amount of the corresponding 4-ethoxy analogue (according to ^{1}H NMR data).
30 (*a*) C. Addicott and C. Wentrup, *Aust. J. Chem.*, 2008, **61**, 592–599; (*b*) A. Reisinger, R. Koch and C. Wentrup, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2247–2249; (*c*) M. Dias, P. Richomme and R. Mornet, *J. Heterocycl. Chem.*, 1996, **33**, 1035–1039; (*d*) V. G. Kartsev and E. M. Gizatullina, *Chem. Heterocycl. Compd.*, 1991, **27**, 672; (*e*) C.-H. Kim and V. E. Marquez, *J. Org. Chem.*, 1987, **52**, 1979–1983; (*f*) H. Balli, M. Huys-Francotte and F. Schmidlin, *Helv. Chim. Acta*, 1987, **70**, 2045–2057.

