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General approach to 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones via nucleophile-mediated ring expansion of tetrahydropyrimidines

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ABSTRACT

A general six-step approach to 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones has been developed. The key step involves a ring expansion reaction of 4-mesyloxymethyl- or 4-tosyloxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one mediated by nucleophilic reagents.

1. Introduction

Monocyclic 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones (e.g., **1**, Fig. 1) are poorly accessible heterocyclic compounds. As for functionalized diazepinones **1**, some of which are useful in the treatment of cardiovascular disorders,[1] hitherto they remain practically

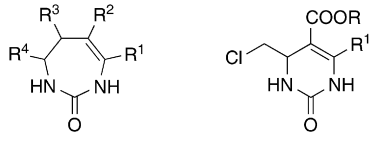
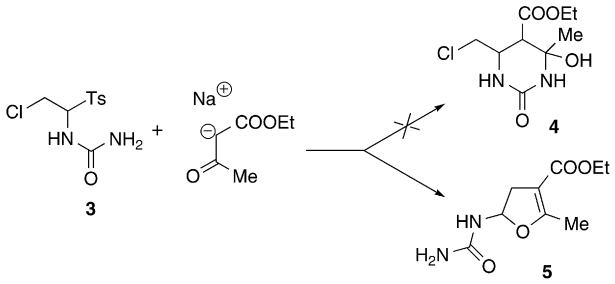


Figure 1. Structures of 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones **1** and 4-chloromethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **2**.

unknown with only rare examples being described in the literature.[1–3] A promising method of their preparation is based on the ring expansion of chloromethyl-substituted tetrahydropyrimidinones **2** (Fig. 1) under the action of external nucleophilic agents to provide esters of 2-oxo-2,3,6,7-tetrahydro-1*H*-1,3-diazepine-5-carboxylic acids.[1,3] The major disadvantage of this approach is the low availability of the starting compounds **2**.[4] This confines application of this approach to synthesis of various diazepines.

Previously, we have developed a general synthesis of 5-functionalized 1,2,3,4-tetrahydropyrimidin-2-ones(thiones) based on the reaction of readily available α-tosyl-substituted *N*-alkylureas or *N*-alkylthioureas with enolates of carbonyl compounds followed by dehydration of obtained 4-hydroxyhexahydropyrimidin-2-ones (thiones).[5] We attempted to synthesize pyrimidines **2** using this approach. However, reaction of urea **3** with the sodium enolate of ethyl acetoacetate led to unexpected formation of 5-ureido-4,5-dihydrofuran **5** (Scheme 1)[6] instead of hydroxypyrimidine **4**. Obviously, formation of compound **5** can be explained by the presence of an additional electrophilic center at β-position to nitrogen in **3**.[7]



Scheme 1. Synthesis of 5-ureido-4,5-dihydrofuran **5** by reaction of urea **3** with the sodium enolate of ethyl acetoacetate.

We hypothesized that α-tosyl-substituted *N*-alkylureas bearing a functional group at β-position (e.g., acyloxy group), which can be transformed into a good leaving group (e.g., Cl, Br, OMs, OTs, etc.) at

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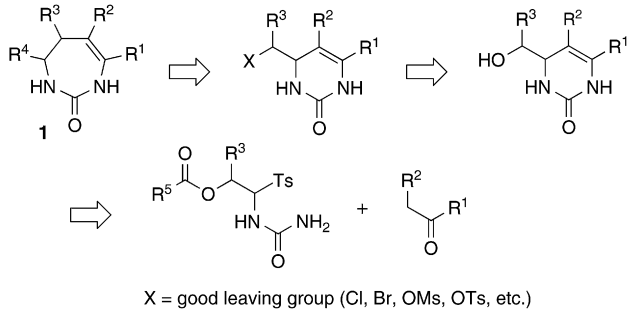
the final stages of synthesis, can serve as starting compounds for the synthesis of diazepines **1**. Our retrosynthetic plan is shown in Scheme 2 and includes preparation of 4-hydroxymethyl-1,2,3,4-tetrahydropyrimidin-2-ones as key compounds.



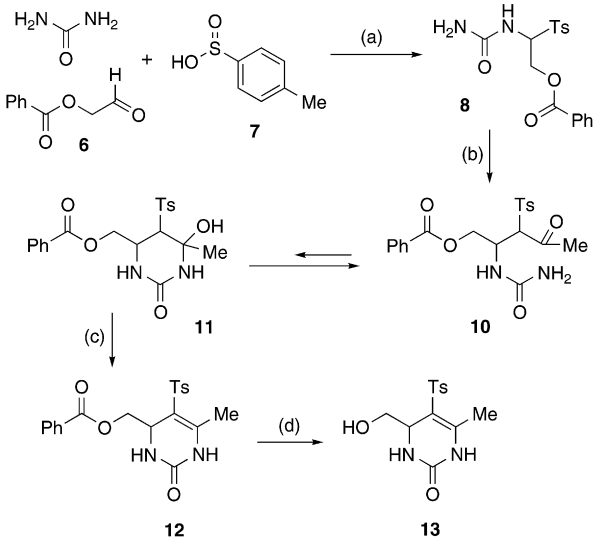
Scheme 2. Retrosynthesis of 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones **1**.

In this communication we describe the application of this strategy to the synthesis of previously unknown 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones.

2. Results and discussion

2.1. Synthesis of 4-mesyloxymethyl- and 4-tosyloxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones

The key precursor for the synthesis of diazepinones, compound **13**, was prepared as shown in Scheme 3. First, readily available **6** was reacted with *p*-toluenesulfinic acid **7** and urea (5 equiv) in water (rt, 7.7 h) to give **8** in 85% yield. A fivefold excess of urea was used to prevent the formation of *N*,*N*′-disubstituted side product (see Ref. 5c). As evidenced by ^{1}H NMR data, the crude **8** was 94% pure and was used in further transformations without additional purification.

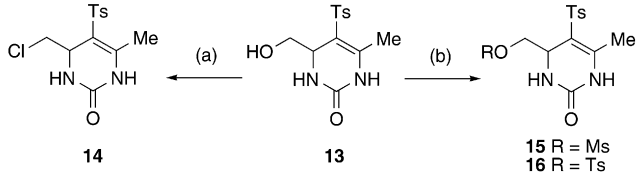


Scheme 3. Synthesis of 4-hydroxymethyl-6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one (**13**). Reagents and conditions: (a) H_2O, rt, 7.7 h, 85%; (b) $TsCH_2C(O)Me$ (**9**), NaH, MeCN, rt, 7.7 h, 84%; (c) 32 mol % TsOH, EtOH, reflux, 3.6 h, 75% or 51 mol % TsOH, MeCN, reflux, 2 h, 93%; (d) KOH, H_2O/EtOH, rt, 1.5 h, 91%.

Tosylacetone **9** was treated with NaH in MeCN to generate the respective Na-enolate, which was reacted with sulfone **8** (MeCN, rt, 7.7 h) to result in the substitution of the tosyl group in **8** and give a product in 84% yield. According to IR in solid phase and NMR in DMSO-d_6, the product structure was assigned to an open-chain oxoalkylurea **10** formed as a mixture of diastereomers (62:38), while the formation of an isomeric cyclic compound **11** did not occur in this instance.

Reflux of compound **10** in EtOH in the presence of TsOH (32 mol %) for 3.6 h led to cyclization of **10** into hydroxypyrimidine **11** followed by its dehydration to give tetrahydropyrimidine **12** in 75% yield. The yield of **12** was further improved (up to 93%) by using a greater amount of TsOH (0.5 equiv) in MeCN as a solvent under the reflux conditions (2 h). The benzoyl protection in **12** was readily removed by treatment with KOH (3 equiv) in EtOH/H_2O to give compound **13** in 91% yield (Scheme 3). Thus, overall yield of **13** from **6** equals 60%.

In order to convert the hydroxyl group in **13** into a good leaving group we first attempted the synthesis of **14** by treatment of **13** with $SOCl_2$ under reflux conditions or with $SOCl_2$ in pyridine at 100 °C (Scheme 4). In both cases we obtained complex reaction mixtures where **14** was contaminated with a variety of by-products.



Scheme 4. Synthesis of 4-chloromethyl- (**14**), 4-mesyloxymethyl- (**15**), and 4-tosyloxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones (**16**). Reagents and conditions: (a) $SOCl_2$, reflux or $SOCl_2$, Py, 100 °C; (b) MsCl or TsCl, DMAP, $CHCl_3$, rt, 96% (for **15**) and 84% (for **16**).

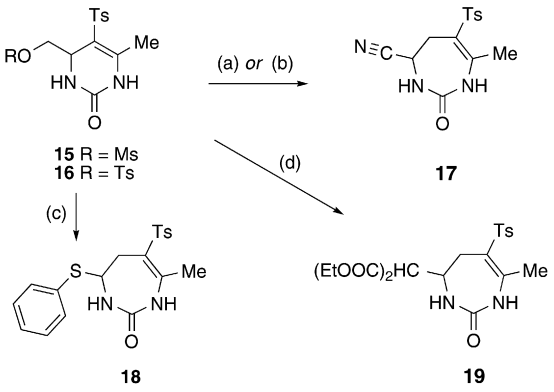
In contrast, treatment of **13** with MsCl or TsCl (DMAP/$CHCl_3$) led to a smooth formation of respective *O*-mesyl- and *O*-tosyl-derivatives **15** and **16** (Scheme 4). Under optimized conditions (**13**/MsCl/DMAP or **13**/TsCl/DMAP in a ratio of 1:2:3) excellent yields of **15** and **16** (96 and 84%, respectively) were obtained, while pyridine and NEt_3 appeared to be ineffective in this instance. For example, the yield of **16** in reaction of **13** with TsCl in pyridine (rt, 5 days) was only 21%.

2.2. Ring expansion of 15 and 16 under nucleophilic conditions to form 1,3-diazepin-2-ones

Ring expansion of 4-chloromethyltetrahydropyrimidin-2-ones **2** under the action of strong nucleophilic agents to form 1,3-diazepin-2-ones has been described in the literature.[3] Similarly, 4-chloromethyl-1,4-dihydropyridines and related compounds have been reported to transform into dihydro- and tetrahydroazepines.[8]

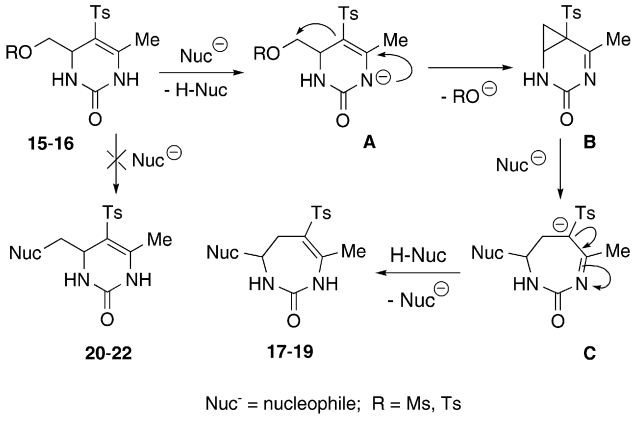
It was reasonable to expect that compounds **15** and **16** would undergo a similar conversion to provide a relatively simple access to novel 4-substituted 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones. Indeed, when treated with NaCN in DMF for 5 h at room temperature, **15** gave 4-cyanodiazepinone **17** in 95% yield (Scheme 5). The latter was also obtained by the reaction of **15** and **16** with NaCN in MeCN plus a catalytic amount of 18-crown-6 (17–30 mol %) for 5.6 and 22.5 h, respectively, at room temperature in excellent yields (Scheme 5). In the absence of 18-crown-6, the progress of the reaction of **15** with NaCN in MeCN as a solvent was dramatically retarded. Under these conditions, after 3 days the reaction mixture consisted of pyrimidine **15** and diazepine **17** (23:77) as evidenced by ^{1}H NMR. The reaction of tosyloxymethylpyrimidine **16** with NaCN in DMSO-d_6 as a solvent was studied by ^{1}H and ^{13}C NMR to reveal no long-lived intermediates. This experiment has shown that the only product of the reaction was diazepinone **17**.

In a similar fashion, compound **15** was reacted with sodium thiophenolate and the sodium salt of diethyl malonate (rt, MeCN) to give diazepinones **18** and **19** in 97% and 95% yields, respectively (Scheme 5).



Scheme 5. Synthesis of 4-substituted 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones **17**–**19**. Reagents and conditions: (a) NaCN, DMF, rt, 5.1 h, 95% (from **15**); (b) NaCN, MeCN, 18-crown-6, rt, 5.6 h, 94% (from **15**) or NaCN, MeCN, 18-crown-6, rt, 22.5 h, 89% (from **16**); (c) PhSH, NaH, rt, 5 h, 97% (from **15**); (d) $CH_2(COOEt)_2$, NaH, rt, 1.5 h, 95% (from **15**).

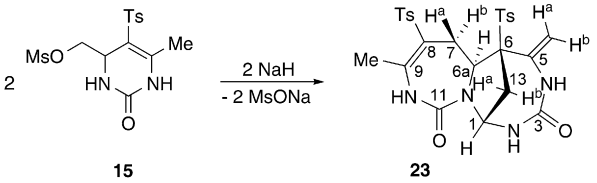
The structures of diazepinones **17**–**19** were unambiguously confirmed by ^{1}H NMR data. The values of coupling constants of N(3)H, 4-H, 5-H(A), and 5-H(B) allowed us to conclude that **17**–**19** exist predominantly in puckered conformation with pseudo axial orientation of substituent at C4. The spectra of **17**–**19** distinctly differ from pyrimidinones **20**–**22** (Scheme 6) whose formation cannot be ruled out a priori. Indeed, a high value of geminal coupling constant between 5-H(A) and 5-H(B) (16.0–16.6 Hz), a rather high value of vicinal coupling constant between N(3)H and 4-H (5.9–6.9 Hz), the long range coupling between 7-CH_3 and one of 5-H (1.2–1.4 Hz) are characteristic of **17**–**19** rather than of their counterparts **20**–**22**. The presence of diazepine ring in **19** was also confirmed by the splitting of methyne proton in $CH(COOEt)_2$ fragment at 3.46 ppm (doublet) uncharacteristic of the respective pyrimidine **22**.



Scheme 6. A plausible pathway for transformation of **15** or **16** into **17**–**19**.

A reasonable mechanism for a transformation of pyrimidines **2** into ethyl 2-oxo-2,3,6,7-tetrahydro-1*H*-1,3-diazepine-5-carboxylates has been reported in the literature.[3b,c] We have hypothesized that the conversion of **15** and **16** into diazepines **17**–**19** under treatment with nucleophilic reagents proceeds in a similar manner (Scheme 6). Upon the proton abstraction from N(1)H, anion **A** undergoes intramolecular nucleophilic substitution to give cyclopropane intermediate **B**. An external strong nucleophile then attacks the most electrophilic bridgehead carbon in **B** to result in the opening of cyclopropane ring and in the formation of diazepinone anion **C**. The latter abstracts proton from the conjugated acid of nucleophilic reagent to give diazepinones **17**–**19**.

Previously we described a stereoselective conversion of ethyl 6-methyl-2-oxo-4-chloromethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate into diethyl 9-methyl-5-methylene-3,11-dioxo-2,3,4,-5,6a,7,10,11-octahydro-1,6-methano[1,3]diazepino[1,7-*e*][1,3,5]triazocine-6,8(1*H*)-dicarboxylate[9] in the presence of strong non-nucleophilic bases (NaH, DBU) as a result of cascade reactions. We have found that this reaction is quite general. Being treated with NaH in MeCN (rt, 3 h) compound **15** afforded tricyclic bis-diaz-epinone **23** in 92% yield (Scheme 7). We suppose that this compound forms by the scheme analogous to that suggested in our previous communication.[9]



Scheme 7. Transformation of 4-mesyloxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one **15** into tricyclic bis-diazepinone **23**.

Bis-diazepinone **23** formed as a single diastereomer with (1*R**,6*S**,6a*S**)-configuration according to ^{1}H–^{1}H ROESY data. NOEs were observed between 7-H^a and 13-H^a and between 6a-H and =CH^a.

3. Conclusion

In summary, a six-step general approach to novel 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones **17**–**19** was developed. It is based on preparation of 4-mesyloxymethyl- **15** or 4-tosyloxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones **16** followed by reaction with nucleophilic reagents (sodium thiophenolate, NaCN, sodium salt of diethyl malonate), which proceeds with ring expansion. In the presence of NaH compound **15** undergoes a cascade reaction resulting in the tricyclic diazepinone **23**.

The starting heterocyclic compound 4-(benzoyloxymethyl)-6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one (**12**) was obtained by the reaction of readily available *N*-[(2-benzoyloxy-1-tosyl)-ethyl]urea (**8**) with tosylacetone in the presence of NaH followed by heterocyclization and dehydration of formed *N*-[(1-benzoyloxy-4-oxo-3-tosyl)but-2-yl]urea (**10**). Hydrolysis of **12** in EtOH/H_2O in the presence of KOH gave 4-hydroxymethyltetrahydropyrimidine **13**, which was converted into the **15** or **16** by reaction with MsCl or TsCl in the presence of DMAP.

An advantage of the developed method is that it can be utilized for synthesis of not only 6-tosyl-substituted but also of other 6-fuctionalyzed tetrahydro-1,3-diazepin-2-ones **1** (see Scheme 2), which will be the subject of forthcoming communications.

4. Experimental section

4.1. General

Acetonitrile was dried by distillation from P_2O_5 and then from CaH_2. Chloroform was purified by distillation over P_2O_5 prior to use. 2-Benzoyloxyethanal (**6**) was synthesized according to modified literature procedure[10] in 40% overall yield by reaction of commercially available dimethyl acetal of 2-chloroethanal with PhCOONa in dry DMF (reflux, 61 h) followed by hydrolysis of the obtained dimethyl acetal of 2-benzoyloxyethanal with 80% aqueous HCOOH (rt, 4 h). *p*-Toluenesulfinic acid (**7**) was synthesized by treatment of a saturated aqueous solution of sodium *p*-toluenesulfinate[11] with hydrochloric acid at 0 °C, dried over P_2O_5, and stored at 0 °C. Sodium hydride (60% suspension in mineral oil) was washed with

anhydrous hexane and dried in vacuo prior to use. All other reagents and solvents were purchased from commercial sources and used without additional purification.

IR spectra (in Nujol or KBr) were recorded on a FTIR Bruker 'Equinox 55/S' spectrophotometer. Peak intensities in the IR spectra are defined as strong (s), medium (m) or weak (w). NMR spectra of synthesized compounds (solutions in DMSO-d_6 and pyridine-d_5) were recorded on a Bruker Avance 600 spectrometer at 600.13 MHz (^{1}H) and 150.90 MHz (^{13}C) and a Bruker DPX 300 spectrometer at 300.13 MHz (^{1}H) and 75.48 MHz (^{13}C). ^{1}H NMR chemical shifts are referenced to the residual proton signal in DMSO-d_6 (2.50 ppm) or pyridine-d_5 (H_α 8.74 ppm). In ^{13}C NMR spectra, signals of DMSO-d_6 (39.50 ppm) or C_γ in pyridine-d_5 (135.91 ppm) were used as a reference. Protons OCH_2, 4-H, and N(3)H for **12**, **15**, and **16** in DMSO-d_6 gave ABCX spin systems, which were analyzed using full-lineshape iteration in gNMR software (v.4.1.0). Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), and some combinations of these, multiplet (m).

Thin layer chromatography (TLC) was performed on silica gel plates Silufol UV 254 (Czech Republic) or Kieselgel 60 F_{254} (Merck) in chloroform/methanol (20:1, v/v) and chloroform/methanol (9:1, v/v) as solvent systems. Spots were visualized with iodine vapors or UV light.

All yields refer to isolated, spectroscopically and TLC pure material.

4.2. *N*-[(2-Benzoyloxy-1-tosyl)ethyl]urea (8)

To a fine emulsion of 2-benzoyloxyethanal (**6**) (3.191 g, 19.44 mmol) in H_2O (25 mL) was added *p*-toluenesulfinic acid (**7**) (3.041 g, 19.47 mmol) under vigorous stirring for 1 min followed by the addition of H_2O (15 mL). After 23 min to the obtained suspension was added urea (5.857 g, 97.53 mmol). The reaction mixture was stirred at room temperature for 7 h 42 min, cooled to 0 °C, the precipitate was filtered off, washed with ice-cold water, light petrol, and dried to give 5.981 g (84.9%) of **8**, which was used without further purification. An analytically pure sample was obtained by recrystallization from MeCN. Mp 127–131 °C (decomp., MeCN). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.86–7.91 (2H, m, $C_{(2)}$H and $C_{(6)}$H in Ph), 7.71–7.76 (2H, m, $C_{(2)}$H and $C_{(6)}$H in 4-MeC_6H_4), 7.64–7.71 (1H, m, $C_{(4)}$H in Ph), 7.49–7.55 (2H, m, $C_{(3)}$H and $C_{(5)}$H in Ph), 7.38–7.44 (2H, m, $C_{(3)}$H and $C_{(5)}$H in 4-MeC_6H_4), 7.13 (1H, d, $^3J_{NH,CH}$=10.4 Hz, N–H), 5.91 (2H, s, NH_2), 5.47 (1H, ddd, $^3J_{CH,NH}$=10.4 Hz, $^3J_{CH,CH(A)}$=4.9 Hz, $^3J_{CH,CH(B)}$=4.7 Hz, CH–N), 4.69 (1H, dd, $^2J_{CH(A),CH(B)}$=12.1 Hz, $^3J_{CH(A),CH}$=4.9 Hz, CH(A) in OCH_2), 4.61 (1H, dd, $^2J_{CH(B),CH(A)}$=12.1 Hz, $^3J_{CH(B),CH}$=4.7 Hz, CH(B) in OCH_2), 2.37 ppm (3H, s, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 165.15 (C=O in PhCOO), 156.50 (N–C=O), 144.72 ($C_{(4)}$ in 4-MeC_6H_4), 134.69 ($C_{(1)}$ in 4-MeC_6H_4), 133.70 ($C_{(4)}$ in Ph), 129.80 ($C_{(2)}$ and $C_{(6)}$ in Ph), 129.46 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 128.94 ($C_{(1)}$ in Ph), 128.77 ($C_{(3)}$ and $C_{(5)}$ in Ph), 128.69 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 68.60 (N–CH), 61.37 (O–CH_2), 21.15 ppm (CH_3). IR (Nujol) ν, cm^{-1}: 3511 s, 3444 s, 3346 s, 3324 s, 3250 m, 3202 m (ν NH), 3060 w (ν CH_{arom}), 1727 s (ν C=O in PhCOO), 1670 s (amide-I), 1597 m (ν CC_{arom}), 1525 s (amide-II), 1492 w (ν CC_{arom}), 1304 m (ν_{as} SO_2), 1271 s (ν C–O), 1128 s (ν_s SO_2), 1115 s (ν C–O), 810 m (δ CH_{arom} in Ts), 749 m, 712 s (δ CH_{arom} in Ph). Anal. Calcd for $C_{17}H_{18}N_2O_5S$: C, 56.34; H, 5.01; N, 7.73. Found: C, 56.61; H, 4.87; N, 7.56.

4.3. *N*-[(1-Benzoyloxy-4-oxo-3-tosyl)but-2-yl]urea (10)

To a mixture of tosylacetone (**9**) (0.633 g, 2.98 mmol) and NaH (0.071 g, 2.96 mmol) was added dry MeCN (7 mL) and the obtained mixture was stirred for 3 min. Then to the resulting solution was added tosylurea **8** (1.077 g, 2.97 mmol). The formed suspension was stirred at room temperature for 7 h 43 min and the solvent was removed in vacuum. To the white solid residue was added a saturated aqueous solution of $NaHCO_3$ (6 mL). The obtained mixture was left overnight at room temperature. Upon cooling to 0 °C, the precipitate was filtered off, washed with ice-cold water, light petrol, cold (−10 °C) ether, and dried to give 1.043 g (83.9%) of **10** as a mixture of diastereomers, 62:38. Mp 145–145.5 °C (EtOH/hexane, 3:1 v/v). ^{1}H NMR of major diastereomer (300.13 MHz, DMSO-d_6) δ: 7.87–7.93 (2H, m, $C_{(2)}$H and $C_{(6)}$H in Ph), 7.73–7.79 (2H, m, $C_{(2)}$H and $C_{(6)}$H in 4-MeC_6H_4), 7.63–7.70 (1H, m, $C_{(4)}$H in Ph), 7.48–7.56 (2H, m, $C_{(3)}$H and $C_{(5)}$H in Ph), 7.38–7.43 (2H, m, $C_{(3)}$H and $C_{(5)}$H in 4-MeC_6H_4), 6.30 (1H, d, $^3J_{NH,CH}$=9.5 Hz, N–H), 5.76 (2H, s, NH_2), 4.97 (1H, d, $^3J_{CH,CH}$=7.9 Hz, CH–SO_2), 4.74 (1H, dddd, $^3J_{CH,NH}$=9.5 Hz, $^3J_{CH,CH}$=7.9 Hz, $^3J_{CH,CH(B)}$=5.6 Hz, $^3J_{CH,CH(A)}$=3.6 Hz, CH–N), 4.37 (1H, dd, $^2J_{CH(A),CH(B)}$=11.4 Hz, $^3J_{CH(A),CH}$=3.6 Hz, CH(A) in OCH_2), 4.25 (1H, dd, $^2J_{CH(B),CH(A)}$=11.4 Hz, $^3J_{CH(B),CH}$=5.6 Hz, CH(B) in OCH_2), 2.35 (3H, s, CH_3 in Ts), 2.26 ppm (3H, s, CH_3 in Ac). ^{1}H NMR of minor diastereomer (300.13 MHz, DMSO-d_6) δ: 7.93–7.99 (2H, m, $C_{(2)}$H and $C_{(6)}$H in Ph), 7.72–7.76 (2H, m, $C_{(2)}$H and $C_{(6)}$H in 4-MeC_6H_4), 7.63–7.70 (1H, m, $C_{(4)}$H in Ph), 7.48–7.56 (2H, m, $C_{(3)}$H and $C_{(5)}$H in Ph), 7.42–7.47 (2H, m, $C_{(3)}$H and $C_{(5)}$H in 4-MeC_6H_4), 6.26 (1H, d, $^3J_{NH,CH}$=8.8 Hz, N–H), 5.69 (2H, s, NH_2), 5.08 (1H, d, $^3J_{CH,CH}$=7.9 Hz, CH–SO_2), 4.50 (1H, dddd, $^3J_{CH,NH}$=8.8 Hz, $^3J_{CH,CH}$=7.9 Hz, $^3J_{CH,CH(B)}$=6.5 Hz, $^3J_{CH,CH(A)}$=4.2 Hz, CH–N), 4.33 (1H, dd, $^2J_{CH(A),CH(B)}$=11.4 Hz, $^3J_{CH(A),CH}$=4.2 Hz, CH(A) in OCH_2), 4.23 (1H, dd, $^2J_{CH(B),CH(A)}$=11.4 Hz, $^3J_{CH(B),CH}$=6.5 Hz, CH(B) in OCH_2), 2.41 (3H, s, CH_3 in Ts), 2.28 ppm (3H, s, CH_3 in Ac). ^{13}C NMR of major diastereomer (75.48 MHz, DMSO-d_6) δ: 199.59 (C=O in Ac), 165.31 (C=O in PhCOO), 157.53 (N–C=O), 145.33 ($C_{(4)}$ in 4-MeC_6H_4), 134.95 ($C_{(1)}$ in 4-MeC_6H_4), 133.49 ($C_{(4)}$ in Ph), 129.92 ($C_{(2)}$ and $C_{(6)}$ in Ph), 129.37 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 129.23 ($C_{(1)}$ in Ph), 128.65 ($C_{(3)}$ and $C_{(5)}$ in Ph), 128.63 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 73.87 (CH–SO_2), 65.65 (O–CH_2), 47.23 (CH–N), 31.57 (CH_3 in Ac), 21.12 ppm (CH_3 in Ts). ^{13}C NMR of minor diastereomer (75.48 MHz, DMSO-d_6) δ: 199.74 (C=O in Ac), 165.36 (C=O in PhCOO), 157.56 (N–C=O), 145.05 ($C_{(4)}$ in 4-MeC_6H_4), 135.33 ($C_{(1)}$ in 4-MeC_6H_4), 133.53 ($C_{(4)}$ in Ph), 129.71 ($C_{(2)}$ and $C_{(6)}$ in Ph), 129.39 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 129.30 ($C_{(1)}$ in Ph), 128.90 ($C_{(3)}$ and $C_{(5)}$ in Ph), 128.72 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 74.15 (CH–SO_2), 64.92 (O–CH_2), 47.72 (CH–N), 32.68 (CH_3 in Ac), 21.18 ppm (CH_3 in Ts). IR (Nujol) ν, cm^{-1}: 3462 s, 3382 s, 3295 s, 3206 m (ν NH), 3061 w (ν CH_{arom}), 1716 s (ν C=O in PhCOO), ~1712 sh (ν C=O in Ac), 1657 s (amide-I), 1596 m (ν CC_{arom}), 1549 s (amide-II), 1496 w (ν CC_{arom}), 1320 s (ν_{as} SO_2), 1277 s (ν C–O), 1154 s (ν_s SO_2), 1116 s (ν C–O), 817 m (δ CH_{arom} in Ts), 764 m, 714 s (δ CH_{arom} in Ph). Anal. Calcd for $C_{20}H_{22}N_2O_6S$: C, 57.40; H, 5.30; N, 6.69. Found: C, 57.20; H, 5.47; N, 6.92.

4.4. 4-(Benzoyloxymethyl)-6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one (12)

A solution of compound **8** (3.356 g, 8.02 mmol) and TsOH·H_2O (0.772 g, 4.06 mmol) in MeCN (53 mL) was refluxed for 2 h under stirring and then solvent was removed in vacuum. To the white solid residue was added saturated aqueous solution of $NaHCO_3$ (8 mL). The obtained suspension was left at room temperature for 2 h. Upon cooling to 0 °C, the precipitate was filtered off, washed with ice-cold water, light petrol, cold (−10 °C) ether, and dried to give 3.000 g (93.4%) of **12**. Mp 223.5–224 °C (decomp., MeCN). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.60 (1H, d, $^4J_{N(1)H,N(3)H}$=1.9 Hz, $N_{(1)}$H), 7.95–8.00 (2H, m, $C_{(2)}$H and $C_{(6)}$H in Ph), 7.74–7.79 (2H, m, $C_{(2)}$H and $C_{(6)}$H in 4-MeC_6H_4), 7.74 (1H, dd, $^3J_{N(3)H,4\text{-}H}$=3.7 Hz, $^4J_{N(3)H,N(1)H}$=1.9 Hz, $N_{(3)}$H), 7.64–7.71 (1H, m, $C_{(4)}$H in Ph), 7.49–7.57 (2H, m, $C_{(3)}$H and $C_{(5)}$H in Ph), 7.38–7.43 (2H, m, $C_{(3)}$H and $C_{(5)}$H in 4-MeC_6H_4), 4.34 (1H, ddd, C part of ABCX spin system, $^3J_{4\text{-}H,CH(B)}$=5.4 Hz, $^3J_{4\text{-}H,N(3)H}$=3.7 Hz, $^3J_{4\text{-}H,CH(A)}$=3.1 Hz, 4-H), 4.27 (1H, dd, B part of ABCX spin system, $^2J_{CH(B),CH(A)}$=10.9 Hz, $^3J_{CH(B),4\text{-}H}$=5.4 Hz, CH(B) in OCH_2), 4.22 (1H, dd, A part of ABCX spin

system, $^{2}J_{CH(A),CH(B)}$=10.9 Hz, $^{3}J_{CH(A),4\text{-}H}$=3.1 Hz, CH(A) in OCH_2), 2.38 (3H, s, CH_3 in Ts), 2.20 ppm (3H, s, 6-CH_3). ^{1}H NMR (300.13 MHz, pyridine-d_5) δ: 11.17 (1H, d, $^{4}J_{N(1)H,N(3)H}$=1.9 Hz, $N_{(1)}H$), 9.29 (1H, dd, $^{3}J_{N(3)H,4\text{-}H}$=3.7 Hz, $^{4}J_{N(3)H,N(1)H}$=1.9 Hz, $N_{(3)}H$), 8.10–8.16 (4H, m, $C_{(2)}H$ and $C_{(6)}H$ in Ph, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.39–7.46 (1H, m, $C_{(4)}H$ in Ph), 7.20–7.31 (4H, m, $C_{(3)}H$ and $C_{(5)}H$ in Ph, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 5.28 (1H, ddd, $^{3}J_{4\text{-}H,CH(B)}$=6.4 Hz, $^{3}J_{4\text{-}H,N(3)H}$=3.7 Hz, $^{3}J_{4\text{-}H,CH(A)}$=3.4 Hz, 4-H), 4.94 (1H, dd, $^{2}J_{CH(B),CH(A)}$=11.1 Hz, $^{3}J_{CH(B),4\text{-}H}$=6.4 Hz, CH(B) in OCH_2), 4.87 (1H, dd, $^{2}J_{CH(A),CH(B)}$=11.1 Hz, $^{3}J_{CH(A),4\text{-}H}$=3.4 Hz, CH(A) in OCH_2), 2.62 and 2.22 ppm (3H and 3H, two s, 6-CH_3, CH_3 in Ts). ^{13}C NMR (75.48 MHz, pyridine-d_5) δ: 166.84 (C=O in PhCOO), 154.39 ($C_{(2)}$), 150.99 ($C_{(6)}$), 144.30 ($C_{(4)}$ in 4-MeC_6H_4), 141.79 ($C_{(1)}$ in 4-MeC_6H_4), 133.60 ($C_{(4)}$ in Ph), 130.82 ($C_{(1)}$ in Ph), 130.63 ($C_{(2)}$ and $C_{(6)}$ in Ph), 130.37 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 128.98 ($C_{(3)}$ and $C_{(5)}$ in Ph), 127.42 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 105.61 ($C_{(5)}$), 68.84 (O–CH_2), 52.30 ($C_{(4)}$), 21.57 (CH_3 in Ts), 17.72 ppm (6-CH_3). IR (Nujol) ν, cm^{-1}: 3362 s, 3202 m, 3114 m (ν NH), 1721 s (ν C=O in PhCOO), 1702 s (amide-I), 1644 s (ν C=C), 1596 w, 1490 w (ν CC_{arom}), 1293 s (ν_{as} SO_2), 1265 s (ν C–O), 1151 s (ν_s SO_2), 1132 s (ν C–O), 813 s (δ CH_{arom} in Ts), 718 s, 702 s (δ CH_{arom} in Ph). Anal. Calcd for $C_{20}H_{20}N_2O_5S$: C, 59.99; H, 5.03; N, 7.00. Found: C, 59.71; H, 5.29; N, 6.97.

4.5. 4-Hydroxymethyl-6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one (13)

To a mixture of KOH (1.231 g, 21.94 mmol) and pyrimidinone **10** (2.900 g, 7.24 mmol) were added EtOH (42 mL) and H_2O (8 mL). The obtained mixture was stirred at room temperature for 1.5 h. Solid substance dissolved in 20 min after mixing. After the reaction was complete, to the formed solution was added AcOH (1 mL) and the solvent was removed in vacuum. To the solid residue was added saturated aqueous solution of $NaHCO_3$ (10 mL). The obtained suspension was left at room temperature for 1 h. Upon cooling to 0 °C, the precipitate was filtered off, washed with ice-cold water, light petrol, and dried to give 1.951 g (90.9%) of **13**. Mp 236–237 °C (decomp., EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.23 (1H, d, $^{4}J_{N(1)H,N(3)H}$=1.9 Hz, $N_{(1)}H$), 7.69–7.74 (2H, m, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.39–7.43 (2H, m, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 7.37 (1H, dd, $^{3}J_{N(3)H,4\text{-}H}$=3.7 Hz, $^{4}J_{N(3)H,N(1)H}$=1.9 Hz, $N_{(3)}H$), 4.99 (1H, t, $^{3}J_{OH,CH2}$=5.5 Hz, OH), 3.88 (1H, dt, $^{3}J_{4\text{-}H,CH2}$=4.7 Hz, $^{3}J_{4\text{-}H,N(3)H}$=3.7 Hz, 4-H), 3.35 (2H, dd, $^{3}J_{CH2,OH}$=5.5 Hz, $^{3}J_{CH2,4\text{-}H}$=4.7 Hz, OCH_2), 2.38 (3H, s, CH_3 in Ts), 2.12 ppm (3H, s, 6-CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 152.62 ($C_{(2)}$), 148.95 ($C_{(6)}$), 143.37 ($C_{(4)}$ in 4-MeC_6H_4), 140.39 ($C_{(1)}$ in 4-MeC_6H_4), 129.95 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 126.14 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 104.04 ($C_{(5)}$), 64.59 (CH_2–OH), 53.32 ($C_{(4)}$), 21.04 (CH_3 in Ts), 16.65 ppm (6-CH_3). IR (Nujol) ν, cm^{-1}: 3479 s (ν OH), 3282 m, 3216 m, 3138 sh, 3090 m (ν NH), 1709 s (amide-I), 1634 s (ν C=C), 1595 w, 1490 w (ν CC_{arom}), 1300 s (ν_{as} SO_2), 1147 s (ν_s SO_2), 1064 s (ν C–O), 815 m (δ CH_{arom}). Anal. Calcd for $C_{13}H_{16}N_2O_4S$: C, 52.69; H, 5.44; N, 9.45. Found: C, 52.82; H, 5.55; N, 9.54.

4.6. 4-Mesyloxymethyl-6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one (15)

To a stirred suspension of hydroxymethylpyrimidine **13** (1.924 g, 6.49 mmol) and DMAP (2.316 g, 18.96 mmol) in dry $CHCl_3$ (10 mL) at 0 °C was added a solution of MsCl (1.485 g, 12.96 mmol) in dry $CHCl_3$ (16 mL) over 4 min. The obtained suspension was stirred for 16 min, the ice bath was removed and stirring continued at room temperature for 45 min. The formed solution was concentrated under vacuum to give a stable foam. Ice-cold water (20 mL) was added to the foam and the oily matter was triturated under cooling until complete crystallization. The precipitate was filtered off, washed with ice-cold water, hexane, and dried to give 2.326 g (95.6%) of **15**. Mp 148.5 °C (decomp., MeCN). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.54 (1H, d, $^{4}J_{N(1)H,N(3)H}$=1.9 Hz, $N_{(1)}H$), 7.74–7.79 (2H, m, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.75 (1H, dd, $^{3}J_{N(3)H,4\text{-}H}$=3.7 Hz, $^{4}J_{N(3)H,N(1)H}$=1.9 Hz, $N_{(3)}H$), 7.40–7.45 (2H, m, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 4.24 (1H, ddd, C part of ABCX spin system, $^{3}J_{4\text{-}H,CH(B)}$=6.0 Hz, $^{3}J_{4\text{-}H,N(3)H}$=3.7 Hz, $^{3}J_{4\text{-}H,CH(A)}$=2.8 Hz, 4-H), 4.17 (1H, dd, B part of ABCX spin system, $^{2}J_{CH(B),CH(A)}$=10.2 Hz, $^{3}J_{CH(B),4\text{-}H}$=6.0 Hz, CH(B) in OCH_2), 4.13 (1H, dd, A part of ABCX spin system, $^{2}J_{CH(A),CH(B)}$=10.2 Hz, $^{3}J_{CH(A),4\text{-}H}$=2.8 Hz, CH(A) in OCH_2), 3.17 (3H, s, CH_3SO_2), 2.39 (3H, s, CH_3 in Ts), 2.18 ppm (3H, s, 6-CH_3). ^{1}H NMR (300.13 MHz, pyridine-d_5) δ: 11.11 (1H, d, $^{4}J_{N(1)H,N(3)H}$=1.9 Hz, $N_{(1)}H$), 9.58 (1H, dd, $^{3}J_{N(3)H,4\text{-}H}$=3.7 Hz, $^{4}J_{N(3)H,N(1)H}$=1.9 Hz, $N_{(3)}H$), 8.05–8.11 (2H, m, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.24–7.30 (2H, m, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 5.16 (1H, ddd, $^{3}J_{4\text{-}H,CH(A)}$=8.0 Hz, $^{3}J_{4\text{-}H,N(3)H}$=3.7 Hz, $^{3}J_{4\text{-}H,CH(B)}$=2.9 Hz, 4-H), 4.89 (1H, dd, $^{2}J_{CH(B),CH(A)}$=10.1 Hz, $^{3}J_{CH(B),4\text{-}H}$=2.9 Hz, CH(B) in OCH_2), 4.75 (1H, dd, $^{2}J_{CH(A),CH(B)}$=10.1 Hz, $^{3}J_{CH(A),4\text{-}H}$=8.0 Hz, CH(A) in OCH_2), 3.28 (3H, s, CH_3SO_2), 2.58 and 2.21 ppm (3H and 3H, two s, 6-CH_3, CH_3 in Ts). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 151.93 ($C_{(2)}$), 150.36 ($C_{(6)}$), 143.79 ($C_{(4)}$ in 4-MeC_6H_4), 139.70 ($C_{(1)}$ in 4-MeC_6H_4), 130.09 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 126.33 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 101.98 ($C_{(5)}$), 72.38 (O–CH_2), 50.39 ($C_{(4)}$), 36.75 (CH_3 in Ms), 21.06 (CH_3 in Ts), 16.66 ppm (6-CH_3). IR (Nujol) ν, cm^{-1}: 3234 br s, 3107 br s (ν NH), 3025 w (ν CH_{arom}), 1727 s (amide-I), 1652 s (ν C=C), 1593 m, 1492 w (ν CC_{arom}), 1354 s (ν_{as} SO_2 in MsO), 1314 s (ν_{as} SO_2 in Ts), 1178 s (ν_s SO_2 in MsO), 1152 s (ν_s SO_2 in Ts), 817 m (δ CH_{arom}). Anal. Calcd for $C_{14}H_{18}N_2O_6S_2$: C, 44.91; H, 4.85; N, 7.48. Found: C, 44.69; H, 5.12; N, 7.34.

4.7. 6-Methyl-5-tosyl-4-tosyloxymethyl-1,2,3,4-tetrahydropyrimidin-2-one (16)

Compound **16** was synthesized in the same way as **15** from hydroxymethylpyrimidinone **13** and TsCl in 84.2% yield. Mp 95–96 °C (toluene/ethyl acetate, 4:1 v/v). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.47 (1H, d, $^{4}J_{N(1)H,N(3)H}$=1.9 Hz, $N_{(1)}H$), 7.73–7.79 (2H, m, $C_{(2)}H$ and $C_{(6)}H$ in 5-Ts or OTs), 7.70 (1H, dd, $^{3}J_{N(3)H,4\text{-}H}$=3.8 Hz, $^{4}J_{N(3)H,N(1)H}$=1.9 Hz, $N_{(3)}H$), 7.62–7.67 (2H, m, $C_{(2)}H$ and $C_{(6)}H$ in OTs or 5-Ts), 7.46–7.52 (2H, m, $C_{(3)}H$ and $C_{(5)}H$ in 5-Ts or OTs), 7.35–7.41 (2H, m, $C_{(3)}H$ and $C_{(5)}H$ in OTs or 5-Ts), 4.09 (1H, ddd, C part of ABCX spin system, $^{3}J_{4\text{-}H,CH(B)}$=6.1 Hz, $^{3}J_{4\text{-}H,N(3)H}$=3.8 Hz, $^{3}J_{4\text{-}H,CH(A)}$=2.9 Hz, 4-H), 3.96 (1H, dd, B part of ABCX spin system, $^{2}J_{CH(B),CH(A)}$=10.0 Hz, $^{3}J_{CH(B),4\text{-}H}$=6.1 Hz, CH(B) in OCH_2), 3.91 (1H, dd, A part of ABCX spin system, $^{2}J_{CH(A),CH(B)}$=10.0 Hz, $^{3}J_{CH(A),4\text{-}H}$=2.9 Hz, CH(A) in OCH_2), 2.44 (3H, s, CH_3 in OTs), 2.38 (3H, s, CH_3 in 5-Ts), 2.15 ppm (3H, s, 6-CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 151.75 ($C_{(2)}$), 150.35 ($C_{(6)}$), 145.03 ($C_{(4)}$ in OTs), 143.68 ($C_{(4)}$ in 5-Ts), 139.54 ($C_{(1)}$ in 5-Ts), 132.00 ($C_{(1)}$ in OTs), 130.20 ($C_{(3)}$ and $C_{(5)}$ in OTs), 129.96 ($C_{(3)}$ and $C_{(5)}$ in 5-Ts), 127.59 ($C_{(2)}$ and $C_{(6)}$ in OTs), 126.17 ($C_{(2)}$ and $C_{(6)}$ in 5-Ts), 101.61 ($C_{(5)}$), 72.35 (O–CH_2), 50.05 ($C_{(4)}$), 21.13 (CH_3 in Ts), 20.99 (CH_3 in Ts), 16.57 ppm (6-CH_3). IR (Nujol) ν, cm^{-1}: 3214 s, 3084 s, 3067 sh (ν NH), 1714 s (amide-I), 1645 s (ν C=C), 1597 m, 1494 w (ν CC_{arom}), 1366 s (ν_{as} SO_2 in TsO), 1317 s (ν_{as} SO_2 in 5-Ts), 1176 s (ν_s SO_2 in TsO), 1155 s (ν_s SO_2 in 5-Ts), 813 s (δ CH_{arom}). Anal. Calcd for $C_{20}H_{22}N_2O_6S_2$: C, 53.32; H, 4.92; N, 6.22. Found: C, 53.44; H, 5.02; N, 6.30.

4.8. 4-Cyano-7-methyl-6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (17)

Method A: to mesyloxymethylpyrimidine **15** (0.574 g, 1.53 mmol) and finely powdered NaCN (0.083 g, 1.69 mmol) was added dry DMF (5 mL). The obtained suspension was stirred at room temperature for 5.1 h, the solvent was removed under high vacuum (temperature of bath not higher then 40 °C), the oily residue was triturated with dry ether until crystallization and the precipitate was filtered off and washed with dry ether. To the

obtained solid substance was added H_2O (3 mL), the obtained suspension was cooled, the precipitate was filtered off, washed with ice-cold water, light petrol, and dried to give 0.444 g (94.8%) of **17**. Mp 213.5–214 °C (decomp., MeOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.99 (1H, d, $^4J_{N(1)H,N(3)H}$=2.0 Hz, $N_{(1)}H$), 8.20 (1H, dd, $^3J_{N(3)H,4\text{-}H}$=6.9 Hz, $^4J_{N(3)H,N(1)H}$=2.0 Hz, $N_{(3)}H$), 7.68–7.74 (2H, m, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.37–7.43 (2H, m, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 4.78 (1H, ddd, $^3J_{4\text{-}H,N(3)H}$=6.9 Hz, $^3J_{4\text{-}H,5\text{-}H(B)}$=5.7 Hz, $^3J_{4\text{-}H,5\text{-}H(A)}$=2.5 Hz, 4-H), 3.35 (1H, dd, $^2J_{5\text{-}H(B),5\text{-}H(A)}$=16.6 Hz, $^3J_{5\text{-}H(B),4\text{-}H}$=5.7 Hz, 5-H(B)), 2.76 (1H, ddq, $^2J_{5\text{-}H(A),5\text{-}H(B)}$=16.6 Hz, $^3J_{5\text{-}H(A),4\text{-}H}$=2.5 Hz, $^5J_{5\text{-}H(A),7\text{-}CH3}$=1.4 Hz, 5-H(A)), 2.38 (3H, s, CH_3 in Ts), 2.16 ppm (3H, d, $^5J_{7\text{-}CH3,5\text{-}H(A)}$=1.4 Hz, 7-$CH_3$). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 154.02 ($C_{(2)}$), 146.26 ($C_{(7)}$), 143.43 ($C_{(4)}$ in 4-MeC_6H_4), 139.73 ($C_{(1)}$ in 4-MeC_6H_4), 129.81 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 126.43 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 118.03 (CN), 112.74 ($C_{(6)}$), 42.11 ($C_{(4)}$), 32.53 ($C_{(5)}$), 21.02 (CH_3 in Ts), 19.91 ppm (7-CH_3). IR (KBr) ν, cm^{-1}: 3372 m, 3280 s, 3122 m (ν NH), 3063 w, 3011 w (ν CH_{arom}), 2244 w (ν CN), 1705 s (amide-I), 1642 s (ν C=C), 1600 w, 1494 m (ν CC_{arom}), 1295 s (ν_{as} SO_2), 1142 s (ν_s SO_2), 815 m (δ CH_{arom}). Anal. Calcd for $C_{14}H_{15}N_3O_3S$: C, 55.07; H, 4.95; N, 13.76. Found: C, 54.93; H, 4.82; N, 13.54.

Method B: a mixture of **15** (0.173 g, 0.46 mmol), finely powdered NaCN (0.026 g, 0.53 mmol), 18-crown-6 (0.021 g, 0.08 mmol) and dry MeCN (3 mL) was stirred at room temperature for 5.6 h. The solvent was removed under vacuum and to the solid residue was added water (1 mL). The obtained suspension was cooled to 0 °C, the precipitate was filtered off, washed with ice-cold water, light petrol, dried, and then washed with ether (2×2 mL) to give 0.132 g (93.6%) of **17**.

Similarly, compound **17** was obtained by reaction of **16** with NaCN in MeCN (rt, 22.5 h) in the presence of 18-crown-6 (30 mol %) in 88.7% yield.

4.9. 7-Methyl-4-phenylthio-6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (18)

To a stirred suspension of NaH (0.028 g, 1.17 mmol) in MeCN (1 mL) was added a solution of thiophenol (0.137 g, 1.24 mmol) in MeCN (3 mL) and the resulting white suspension was stirred at room temperature for 17 min. Mesyloxymethylpyrimidine **15** (0.409 g, 1.09 mmol) and MeCN (1 mL) were added and the obtained suspension was stirred at room temperature for 5 h. After the reaction was complete the solvent was removed under vacuum, the oily residue was triturated with light petrol (3×5 mL), H_2O (2 mL) was added and the residue was triturated under cooling until complete crystallization. The formed suspension was cooled, the precipitate was filtered off, washed with ice-cold water, light petrol, and dried to give 0.407 g (97.1%) of **18**. Mp 160–160.5 °C (EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.84 (1H, d, $^4J_{N(1)H,N(3)H}$=1.9 Hz, $N_{(1)}H$), 8.27 (1H, dd, $^3J_{N(3)H,4\text{-}H}$=6.1 Hz, $^4J_{N(3)H,N(1)H}$=1.9 Hz, $N_{(3)}H$), 7.67–7.73 (2H, m, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.25–7.44 (5H, m, Ph), 7.37–7.42 (2H, m, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 4.97 (1H, ddd, $^3J_{4\text{-}H,N(3)H}$=6.1 Hz, $^3J_{4\text{-}H,5\text{-}H(B)}$=6.1 Hz, $^3J_{4\text{-}H,5\text{-}H(A)}$=2.4 Hz, 4-H), 3.35 (1H, dd, $^2J_{5\text{-}H(B),5\text{-}H(A)}$=16.0 Hz, $^3J_{5\text{-}H(B),4\text{-}H}$=6.1 Hz, 5-H(B)), 2.87 (1H, ddq, $^2J_{5\text{-}H(A),5\text{-}H(B)}$=16.0 Hz, $^3J_{5\text{-}H(A),4\text{-}H}$=2.4 Hz, $^5J_{5\text{-}H(A),7\text{-}CH3}$=1.2 Hz, 5-H(A)), 2.38 (3H, s, CH_3 in Ts), 2.15 ppm (3H, d, $^5J_{7\text{-}CH3,5\text{-}H(A)}$=1.2 Hz, 7-$CH_3$). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 154.11 ($C_{(2)}$), 145.99 ($C_{(7)}$), 143.21 ($C_{(4)}$ in 4-MeC_6H_4), 139.97 ($C_{(1)}$ in 4-MeC_6H_4), 133.56 ($C_{(1)}$ in SPh), 131.63 ($C_{(2)}$ and $C_{(6)}$ in SPh), 129.70 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 129.06 ($C_{(3)}$ and $C_{(5)}$ in SPh), 127.24 ($C_{(4)}$ in SPh), 126.54 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 112.51 ($C_{(6)}$), 58.72 ($C_{(4)}$), 35.63 ($C_{(5)}$), 21.02 (CH_3 in Ts), 19.89 ppm (7-CH_3). IR (Nujol) ν, cm^{-1}: 3217 s, 3142 m, 3062 s (ν NH), 1681 s (amide-I), 1629 s (ν C=C), 1296 s (ν_{as} SO_2), 1146 s (ν_s SO_2), 814 m (δ CH_{arom} in Ts), 751 s, 691 s (δ CH_{arom} in Ph). Anal. Calcd for $C_{19}H_{20}N_2O_3S_2$: C, 58.74; H, 5.19; N, 7.21. Found: C, 58.52; H, 5.29; N, 7.02.

4.10. 4-[Di(ethoxycarbonyl)methyl]-7-methyl-6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (19)

To a stirred suspension of NaH (0.047 g, 1.96 mmol) in dry MeCN (2 mL) at 0 °C was added a solution of diethyl malonate (0.323 g, 2.02 mmol) in dry MeCN (5 mL) over 2 min. The obtained white suspension was stirred for 10 min, then mesyloxymethylpyrimidine **15** (0.646 g, 1.73 mmol) and MeCN (3 mL) were added. The reaction mixture was stirred at room temperature for 1 h 27 min, the solvent was removed under vacuum and the oily residue was triturated with light petrol until crystallization. A saturated aqueous solution of $NaHCO_3$ (2 mL) was added, the obtained suspension was cooled, the precipitate was filtered off, washed with ice-cold water, light petrol, and dried to give 0.720 g (95.4%) of **19**. Mp 150–151 °C (ethyl acetate). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.74 (1H, d, $^4J_{N(1)H,N(3)H}$=1.7 Hz, $N_{(1)}H$), 7.60–7.66 (2H, m, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.62 (1H, dd, $^3J_{N(3)H,4\text{-}H}$=5.9 Hz, $^4J_{N(3)H,N(1)H}$=1.7 Hz, $N_{(3)}H$), 7.37–7.43 (2H, m, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 3.98–4.20 (4H, m, two OCH_2), 3.86 (1H, dddd, $^3J_{4\text{-}H,CH}$=9.8 Hz, $^3J_{4\text{-}H,5\text{-}H(B)}$=6.4 Hz, $^3J_{4\text{-}H,N(3)H}$=5.9 Hz, $^3J_{4\text{-}H,5\text{-}H(A)}$=2.2 Hz, 4-H), 3.46 (1H, d, $^3J_{CH,4\text{-}H}$=9.8 Hz, CH in $CH(COOEt)_2$), 2.95 (1H, dd, $^2J_{5\text{-}H(B),5\text{-}H(A)}$=16.0 Hz, $^3J_{5\text{-}H(B),4\text{-}H}$=6.4 Hz, 5-H(B)), 2.60 (1H, ddq, $^2J_{5\text{-}H(A),5\text{-}H(B)}$=16.0 Hz, $^3J_{5\text{-}H(A),4\text{-}H}$=2.2 Hz, $^5J_{5\text{-}H(A),7\text{-}CH3}$=1.4 Hz, 5-H(A)), 2.38 (3H, s, CH_3 in Ts), 2.20 (3H, br s, 7-CH_3), 1.17 (3H, t, $^3J_{CH3,CH2}$=7.1 Hz, CH_3 in OEt), 1.16 ppm (3H, t, $^3J_{CH3,CH2}$=7.1 Hz, CH_3 in OEt). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 166.75 (C=O in COOEt), 166.34 (C=O in COOEt), 154.47 ($C_{(2)}$), 146.27 ($C_{(7)}$), 143.33 ($C_{(4)}$ in 4-MeC_6H_4), 139.67 ($C_{(1)}$ in 4-MeC_6H_4), 129.88 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 126.28 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 111.98 ($C_{(6)}$), 61.48 (O–CH_2), 61.34 (O–CH_2), 55.21 (CH in $CH(COOEt)_2$), 50.11 ($C_{(4)}$), 31.73 ($C_{(5)}$), 21.01 (CH_3 in Ts), 19.67 (7-CH_3), 13.79 ppm (CH_3 in COOEt). IR (Nujol) ν, cm^{-1}: 3361 m, 3298 s, 3274 s, 3223 s, 3143 m, 3109 s (ν NH), 1742 m, 1721 s (ν C=O in COOEt), 1690 s (amide-I), 1639 s (ν C=C), 1599 w, 1494 w (ν CC_{arom}), 1312 s (ν_{as} SO_2), 1264 s, 1185 s (ν C–O), 1150 s (ν_s SO_2), 813 m (δ CH_{arom}). Anal. Calcd for $C_{20}H_{26}N_2O_7S$: C, 54.78; H, 5.98; N, 6.39. Found: C, 54.53; H, 6.21; N, 6.42.

4.11. 9-Methyl-5-methylene-6,8-ditosyl-1,2,4,5,6,6a,7,10-octahydro-1,6-methano[1,3]diazepino[1,7-*e*][1,3,5]triazocine-3,11-dione (23)

To a mixture of NaH (0.084 g, 3.50 mmol) and mesyloxymethylpyrimidine **15** (1.170 g, 3.12 mmol) was added dry MeCN (9.6 mL). The obtained suspension was stirred in an ice bath for 15 min and then at room temperature for 3 h and the solvent was removed under vacuum. To the solid residue was added water (3 mL) and to the formed suspension was added 2% HCl to pH 6. A saturated aqueous solution of $NaHCO_3$ (3 mL) was added, the suspension was cooled, the precipitate was filtered off, washed with ice-cold water, light petrol, and dried to give 0.799 g (91.9%) of **23**. Mp >300 °C (decomp., DMF). ^{1}H NMR (600.13 MHz, DMSO-d_6) δ: 8.79 (1H, s, $N_{(10)}H$), 7.84 (1H, d, $^4J_{N(4)H,N(2)H}$=2.0 Hz, $N_{(4)}H$), 7.74–7.77 (2H, m, $C_{(2)}H$ and $C_{(6)}H$ in 6-Ts), 7.66–7.69 (2H, m, $C_{(2)}H$ and $C_{(6)}H$ in 8-Ts), 7.42–7.46 (4H, m, $C_{(3)}H$ and $C_{(5)}H$ in 6-Ts and 8-Ts), 7.26 (1H, dd, $^3J_{N(2)H,1\text{-}H}$=6.5 Hz, $^4J_{N(2)H,N(4)H}$=2.0 Hz, $N_{(2)}H$), 5.37 (1H, s, CH(a) in =CH_2), 5.12 (1H, dd, $^3J_{1\text{-}H,13\text{-}H(a)}$=7.9 Hz, $^3J_{1\text{-}H,\ N(2)H}$=6.5 Hz, 1-H), 5.11 (1H, s, CH(b) in =CH_2), 4.03 (1H, d, $^3J_{6a\text{-}H,7\text{-}H(a)}$=9.7 Hz, 6a-H), 3.91 (1H, d, $^2J_{7\text{-}H(b),7\text{-}H(a)}$=16.5 Hz, 7-H(b)), 2.93 (1H, dd, $^2J_{13\text{-}H(a),13\text{-}H(b)}$=12.7 Hz, $^3J_{13\text{-}H(a),1\text{-}H}$=7.9 Hz, 13-H(a)), 2.77 (1H, ddq, $^2J_{7\text{-}H(a),7\text{-}H(b)}$=16.5 Hz, $^3J_{7\text{-}H(a),6a\text{-}H}$=9.7 Hz, $^5J_{7\text{-}H(a),9\text{-}CH3}$=1.7 Hz, 7-H(a)), 2.43 and 2.41 (3H and 3H, two s, CH_3 in 6-Ts and 8-Ts), 2.37 (1H, d, $^2J_{13\text{-}H(b),13\text{-}H(a)}$=12.7 Hz, 13-H(b)), 2.15 ppm (3H, d, $^5J_{9\text{-}CH3,7\text{-}H(a)}$=1.7 Hz, 9-$CH_3$). ^{13}C NMR (150.90 MHz, DMSO-d_6) δ: 156.13 ($C_{(3)}$), 152.66 ($C_{(11)}$), 144.98, 144.91, 143.16 and 142.18 ($C_{(5)}$, $C_{(9)}$, $C_{(4)}$ in 6-Ts, $C_{(4)}$ in 8-Ts), 140.23 ($C_{(1)}$ in 8-Ts), 133.42 ($C_{(1)}$ in 6-Ts), 130.18 ($C_{(3)}$ and $C_{(5)}$ in 6-Ts), 129.74 ($C_{(3)}$ and $C_{(5)}$ in 8-Ts),

129.64 ($C_{(2)}$ and $C_{(6)}$ in 6-Ts), 126.06 ($C_{(2)}$ and $C_{(6)}$ in 8-Ts), 113.66 ($C_{(8)}$), 109.85 (=CH_2), 74.84 ($C_{(6)}$), 67.82 ($C_{(1)}$), 64.03 ($C_{(6a)}$), 32.76 and 32.37 ($C_{(7)}$, $C_{(13)}$), 21.12 and 20.95 (CH_3 in 6-Ts and 8-Ts), 20.28 ppm (9-CH_3). IR (Nujol) ν, cm^{-1}: 3353 s, 3211 s, 3115 s, 3093 s (ν NH), 1698 s, 1669 s (amide-I), 1631 s (ν C=C), 1599 w (ν CC_{arom}), 1302 s (ν_{as} SO_2), 1139 s (ν_s SO_2), 914 m (δ =CH_2), 821 m (δ CH_{arom}). Anal. Calcd for $C_{26}H_{28}N_4O_6S_2$: C, 56.10; H, 5.07; N, 10.07. Found: C, 55.85; H, 5.35; N, 9.78.

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