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Nucleophile-mediated ring expansion of 4-chloromethyl- and 4-mesyloxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones to 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones: effect of the leaving group and the substituent at C6

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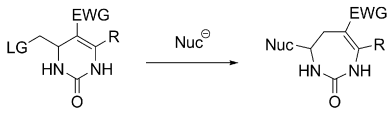
ABSTRACT

A five-step synthesis of 4-chloromethyl- and 4-mesyloxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones has been developed. The reaction of *N*-[(2-benzoyloxy-1-tosyl)ethyl]urea with sodium enolates of α-tosylketones followed by cyclization–dehydration, and debenzoylation gave 4-hydroxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones, which were transformed into the 4-chloromethyl- or 4-mesyloxymethyl-derivatives. Treatment of the latter with nucleophilic reagents, such as sodium cyanide, sodium diethyl malonate, sodium thiophenolate, or potassium phthalimide, afforded the corresponding 4,7-disubstituted 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones as a result of ring expansion. The effect of the leaving group and the substitution at the position C6 on the reactivity of the pyrimidines is discussed.

1. Introduction

Monocyclic 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones, particularly 6-functionalized ones (e.g., **1**, Scheme 1), are a poorly studied class of heterocycles. A limited number of alkyl 2-oxo-2,3,6,7-tetrahydro-1*H*-1,3-diazepine-5-carboxylates (**1** EWG=COOR′) useful in the treatment of cardiovascular disorders[1] were synthesized by the ring expansion of 4-chloromethyl-substituted tetrahydropyrimidinones **2** (LG=Cl, EWG=COOR′) under the action of nucleophiles (Scheme 1).[1,2] However, this synthesis suffers from a poor availability of starting materials. Thus far, 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%).[2b,c] This limits application of the above approach to synthesis of tetrahydrodiazepinones.



2 1

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

Recently, we have developed a general and convenient approach to 5-functionalized 1,2,3,4-tetrahydropyrimidin-2-ones/thiones from readily available α-tosyl-substituted *N*-alkylureas or *N*-alkylthioureas and enolates of carbonyl compounds.[3] Using this method, we have prepared 4-tosyloxymethyl- and 4-mesyloxymethyl-6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones (**2** LG=OTs, OMs; EWG=Ts; R=Me) and demonstrated that they can serve as precursors for the synthesis of the previously unknown tetrahydrodiazepinones (**1** EWG=Ts, R=Me).[4] Encouraged by the results obtained, we further investigated the synthesis of diazepines **1** from pyrimidines **2** with various leaving groups **LG** and C6-substituents. In this paper, we describe the reactivity of 6-phenyl- and 6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones **2** towards selected *C*-, *N*- and *S*-nucleophiles with the objective of the efficient preparation of novel 7-phenyl- and 7-methyl-6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones.

2. Results and discussion

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

4-Hydroxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones served as key compounds for the synthesis of diazepinones. Preparation of the previously unknown 6-phenyl derivative **3** starting from readily available *N*-[(2-benzoyloxy-1-tosyl)ethyl]urea (**4**)[4] is shown in Scheme 2.

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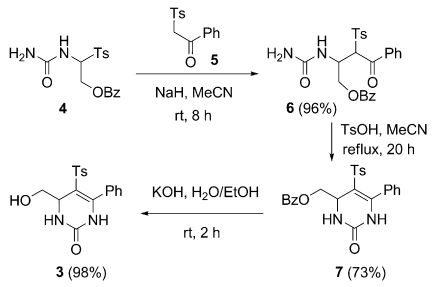
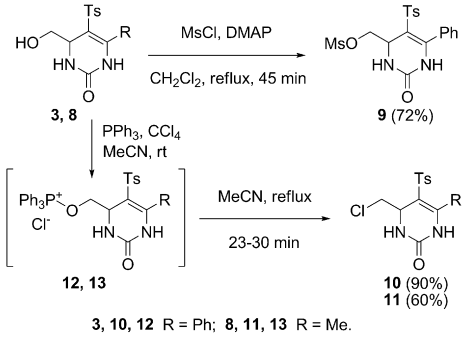


Scheme 2. Synthesis of 4-hydroxymethyl-6-phenyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one (**3**).

The reaction of **4** with the sodium enolate of tosylacetophenone (**5**) in dry MeCN at rt for 8 h gave the product of tosyl group substitution, urea **6**, in 96% yield as a mixture of two diastereomers in a ratio of 59:41. Heterocyclization–dehydration of **6** in refluxing MeCN in the presence of TsOH resulted in pyrimidinone **7** in 73% yield. In contrast to *N*-[(1-benzoyloxy-4-oxo-3-tosyl)pent-2-yl] urea,[4] this transformation proceeded under more drastic conditions. A 3-fold excess of TsOH and a long reaction time (20 h) were necessary for completion of the reaction. This can be explained by the reduced electrophilicity of the benzoyl group compared with the acetyl group. The benzoyl protection in **7** was removed by treatment with KOH (3 equiv) in EtOH/H_2O at rt for 2 h to give compound **3** in 98% yield. Thus, the overall yield of **3** from **4** was 69%.

The next step was the transformation of hydroxymethylpyrimidines **3** and **8**[4] into compounds **9**, **10** and **11** containing two different, good leaving groups (MsO and Cl) (Scheme 3).



Scheme 3. Synthesis of 4-mesyloxymethyl-**9** and 4-chloromethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones **10**, **11**.

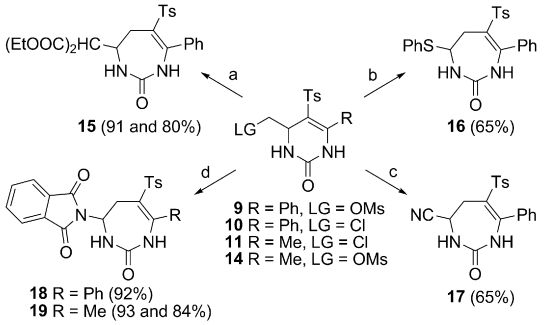
Mesylation of **3** using the procedure applied for 4-hydroxymethylpyrimidine **8** (MsCl, DMAP, $CHCl_3$, rt, 1 h)[4] did not complete even when the reaction time was prolonged up to 20 h. Reflux of reaction mixture in $CHCl_3$ (**3**/MsCl/DMAP in a ratio of 1:2:3) for 15 min led to complete transformation of **3** into **9**. However, excesses of the reagents and elevated temperature resulted in formation of some side products, which complicated the isolation of **9**. To improve the reaction, we varied solvents, reaction time and temperature, the ratios of the reagents. Under the optimized conditions (**3**/MsCl/DMAP in a ratio of 1:2:3, CH_2Cl_2, reflux for 45 min) and after crystallization mesyloxymethylpyrimidine **9** was obtained in 72% yield.

Since previously we have demonstrated that $SOCl_2$ with or without bases gave unsatisfactory results for preparation of chloromethylpyrimidine **11** from **8**[4] to prepare compound **10** from **3**, PPh_3/CCl_4 was used.[5] When **3** was treated with PPh_3 (1.25 equiv) and CCl_4 (2.0 equiv) in MeCN at rt for 4 h, the initial suspension turned into a solution, and no starting pyrimidine was detected by TLC. Then MeCN was removed in vacuum and the residue was dissolved in $CHCl_3$. Washing with water had no visual effect on this solution, however immediate precipitation occurred after washing with saturated aqueous solution of $NaHCO_3$. The precipitate was filtered, and an almost quantitative amount of starting compound **3** was recovered. These observations suggest that the reaction of **3** with PPh_3 and CCl_4 gives stable oxyphosphonium intermediate **12**, which does not convert into chloromethyl derivative **10** at rt and after treatment with aqueous $NaHCO_3$ hydrolyses to **3**. However, reflux of **3**, PPh_3 and CCl_4 in MeCN for 23 min led to smooth formation of **10** in 90% yield, which precipitated from the reaction mixture and was isolated by filtration.

We also applied the above conditions (1.25 equiv of PPh_3, 2.0 equiv of CCl_4, MeCN, reflux) for preparation of chloromethylpyrimidine **11** from **8**. The reaction completed in 30 min, and the desired product was isolated using column chromatography on silica gel in 60% yield. Therefore, mesylation of **8**, which proceeds in 96% yield[4] is preferable for transformation of the hydroxyl group into a good leaving group.

2.2. Synthesis of 4,7-disubstituted 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones

The reaction of tetrahydropyrimidines **9**, **10**, **11** and described earlier **14**[4] with nucleophilic reagents (sodium diethyl malonate, PhSNa, NaCN and potassium phthalimide) proceeding with one-carbon ring expansion is the final step of the diazepine synthesis (Scheme 4).



Scheme 4. Synthesis of 4-substituted 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones **15**–**19**. Reagents and conditions: (a) $NaCH(COOEt)_2$, MeCN, rt, 4 h (for **9**) or 4.5 h (for **10**) (b) NaSPh, MeCN, rt, 4 h (for **9**) or 5 h (for **10**); (c) NaCN, DMF, rt, 1.5 h; (d) potassium phthalimide, MeCN, reflux, 15 min for **18** (from **9**), 15 min for **19** (from **14**) and 50 min (from **11**).

Reaction of **9** and **10** with sodium diethyl malonate (1.27 equiv) generated by treatment of diethyl malonate solution in MeCN by NaH smoothly proceeded at rt for 4–4.5 h affording diazepinone **15** in 91 and 80% yields, respectively.

Chloromethylpyrimidine **10** readily reacted with sodium thiophenolate (**10**/NaSPh in ratio of 1.0:1.5) in MeCN at rt for 5 h to produce compound **16** in 65% overall yield after purification by column chromatography on silica gel. At a 1.0:1.1 ratio of **10** to NaSPh, it was necessary to reflux the reaction mixture for 1 h after stirring at rt for 5 h. The reaction of mesyloxymethylpyrimidine **9** with this nucleophile completed at rt for 4 h when the ratio **9**/NaSPh was 1.00:1.12. Under the conditions described the purity of product **16** was the same according to the ^1H NMR spectroscopic data of crude isolated materials.

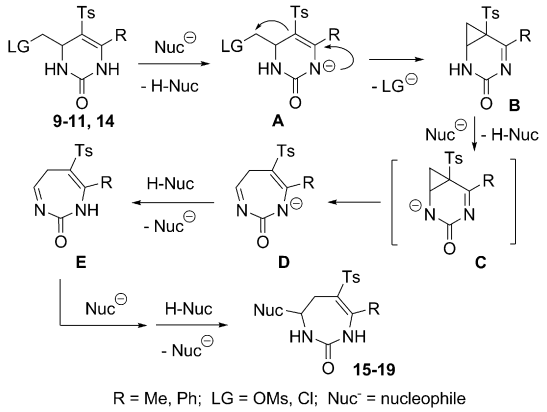
We have shown that mesyloxymethylpyrimidine **14** readily reacts with NaCN in MeCN in the presence of 18-crown-6 to give the corresponding diazepinone.[4] These conditions were used to prepare diazepinone **17** from **9**, but the reaction did not proceed at rt. Reflux of the reaction mixture for 3.8 h (**9**/NaCN/18-crown-6 in a ratio of 1.0:1.5:0.2) led to conversion of **9** into an unidentified mixture of products. However, the reaction of **9** with NaCN (**9**/NaCN

in a ratio of 1.0:1.3) proceeded in DMF at rt for 1.5 h and gave compound **17** in 65% yield. Under these conditions conversion of chloromethylpyrimidine **10** into **17** did not complete even after 9.5 h. Reaction of **10** with NaCN (**10**/NaCN in a ratio of 1.0:1.5) in DMF at 40 °C for 1.5 h afforded diazepinone **17**. According to ^{1}H NMR spectroscopy, the isolated crude material contained more impurities compared with the crude product obtained from **9**. Since the intermediate compounds, which form from alcohols, PPh_3 and CCl_4 can react with external nucleophiles,[6] we tried to react solution of **12** in MeCN (see above) with NaCN in the presence of 18-crown-6. The reaction did not proceed at rt, and after reflux the only isolated product was chloromethylpyrimidine **10**.

4-Phthalimido-substituted diazepinone **18** was prepared by the reaction of compound **9** with potassium phthalimide in refluxing MeCN in 92% yield. In contrast, Cl-derivative **10** remained practically intact after 10 h of reflux with potassium phthalimide in MeCN. With DMF as a solvent the reaction of **10** with potassium phthalimide did not proceed at rt, and only various side products were formed instead of desired diazepine **18** when the reaction mixture was heated to 45 °C. Diazepinone **19** was obtained by the reaction of mesyloxymethylpyrimidine **14** and chloromethylpyrimidine **11** with potassium phthalimide (MeCN, reflux) in 93 and 84% yields, respectively, but in the case of **11** the reaction time was longer than for **14**.

Thus, with all studied nucleophiles mesyloxypyrimidines **9** and **14** are more suitable starting materials for the diazepine synthesis compared with the corresponding chloropyrimidines **10** and **11** because of their greater availability and higher reactivity. The presence of a phenyl group at position 6 in starting pyrimidines (**9** and **10**) decreases the yields of the corresponding diazepines compared with 6-methylpyrimidines (**11** and **14**) when NaCN and NaSPh were used as nucleophiles. Moreover, in contrast to pyrimidines **2** (Scheme 1, R=Me), which readily reacted with NaH[4,7] and Grignard reagents,[1,2d] compounds **9** and **10** treated with NaH or MeMgI under various conditions did not react or complex mixtures of unidentified products formed.

A reasonable mechanism for a transformation of pyrimidines **9**–**11**, **14** into diazepines **15**–**19** is shown in Scheme 5. Upon the proton abstraction from $N_{(1)}$H under the action of nucleophile, anions **A** undergo intramolecular nucleophilic substitution to give cyclopropane intermediates **B**. Deprotonation of the latter lead to extremely unstable anions C, which spontaneously, via ring expansion, convert into diazepine anions **D**, and then into 2,5-dihydro-1*H*-1,3-diazepin-2-ones **E**. Following nucleophilic addition to acylimines **E** gives the final products. This mechanism is confirmed by the results of our previous works,[4,7,8] detailed ab initio calculations (B3LYP/6-31+G**),[9] and it is in good agreement with the literature data.[2,10]



Scheme 5. A plausible pathway for transformation of **9**–**11**, **14** into **15**–**19**.

An alternative mechanism of the above ring expansion could include formation of bicyclic aziridine intermediates after deprotonation of $N_{(3)}$H and following intramolecular nucleophilic substitution. However this route would result in attachment of the nucleophile at C(5) rather than C(4) as found.

The structures of diazepinones **15**–**17** were confirmed by ^{1}H NMR spectroscopy as described elsewhere.[4] Indeed, a high value of geminal coupling constant between 5-$H_{(A)}$ and 5-$H_{(B)}$ (15.8–16.6 Hz) and a rather high value of vicinal coupling constant between $N_{(3)}$H and 4-H (5.1–6.7 Hz) are characteristics of the diazepine ring of **15**–**17**. Splitting of the methine proton in the $CH(COOEt)_2$ fragment at 3.73 ppm (doublet) in **15** also confirms its diazepine structure. Formation of diazepine ring for compounds **18** and **19** is unambiguously confirmed by the value of $C_{(4)}$ chemical shift in the ^{13}C NMR spectra, which is 61.50 and 61.13 ppm, respectively. Chemical shift of $C_{(4)}$ for the corresponding pyrimidines, which could result from a direct nucleophilic substitution of leaving groups in **9**–**11**, **14** is expected to be about 45 ppm.[11,12] The coupling constants of $N_{(3)}$H, 4-H, 5-$H_{(A)}$ and 5-$H_{(B)}$ in the ^{1}H NMR spectra of **15**–**17** in DMSO-d_6 ($^3J_{N(3)H,4\text{-}H}$=5.1–6.7 Hz, $^3J_{4\text{-}H,5\text{-}H(A)}$=5.7–7.3 Hz and $^3J_{4\text{-}H,5\text{-}H(B)}$=2.4–2.7 Hz) allowed us to conclude that they exist predominantly in a puckered conformation with a pseudo axial orientation of the substituent at $C_{(4)}$. ^{1}H NMR spectroscopic characteristics of 4-phthalimido-substituted diazepines **18** and **19** significantly differ from those described for compounds **15**–**17**. Thus, a lower geminal coupling constant between 5-$H_{(A)}$ and 5-$H_{(B)}$ (14.6–15.0 Hz), low vicinal coupling constant between $N_{(3)}$H and 4-H (1.9–2.7 Hz), two very different vicinal coupling constants between 5-$H_{(A)}$ and 4-H (9.1–9.9 Hz) and 5-$H_{(B)}$ and 4-H (2.5–3.2 Hz) indicate that diazepines **18** and **19** in DMSO-d_6 exist predominantly in a puckered conformation with a pseudo equatorial orientation of the phthalimide moiety. These conclusions agree with quantum mechanical calculations for **15**–**19** using semiempirical method PM6.[13]

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 was described. It is based on preparation of 4-mesyloxymethyl- or 4-chloromethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones followed by reaction with nucleophilic reagents (sodium thiophenolate, NaCN, sodium diethyl malonate or potassium phthalimide), which proceeds with ring expansion. The key intermediate heterocyclic compounds 4-hydroxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones were obtained by ureidoalkylation of α-tosyl-substituted ketones followed by heterocyclization–dehydration of products and subsequent hydrolysis. They were converted into diazepine precursors by reaction with MsCl/DMAP or with PPh_3/CCl_4. The advantage of our approach is that it allows preparation of starting pyrimidines (**2**, Scheme 1) with different leaving groups and various substituents at positions 5 and 6. These pyrimidines can be utilized for synthesis of a large variety of functionalized tetrahydro-1,3-diazepin-2-ones, which will be the subject of forthcoming publications.

4. Experimental section

4.1. General

Acetonitrile was dried by distillation from P_2O_5 and then from CaH_2. Dichloromethane and tetrachloromethane were purified by distillation over P_2O_5 prior to use. Sodium hydride (60% suspension in mineral oil) was washed with anhydrous hexane and dried in vacuum prior to use. All other reagents and solvents were purchased from commercial sources and used without additional

purification. IR spectra (in Nujol) were recorded using a Bruker Vector 22 spectrophotometer. Peak intensities in the IR spectra are defined as very strong (vs), strong (s), medium (m) or weak (w). ^{1}H and ^{13}C NMR spectra of synthesized compounds (solutions in DMSO-d_6) were recorded on 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, 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). Column chromatography was performed using Merck silica gel 60 (0.04–0.063 mm). Thin layer chromatography (TLC) was performed on silica gel plates Kieselgel 60 F_{254} (Merck) in chloroform/methanol (20:1, v/v) and chloroform/methanol (9:1, v/v). Spots were visualized with iodine vapours or UV light. All yields refer to isolated, spectroscopically and TLC pure compounds.

*4.1.1. 4-(Hydroxymethyl)-6-phenyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one (**3**).* To a solution of KOH (1.589 g, 28.32 mmol) in H_2O (9 mL) were added pyrimidinone **7** (4.366 g, 9.44 mmol) and EtOH (31.4 mL). The obtained mixture was stirred at rt for 2 h. In 30 min after mixing solid substance dissolved and after additional 25 min new precipitate occurred. After the reaction was complete, the formed suspension was acidified with 18% aqueous HCl to pH 6 and the solvent was removed in vacuum. To the solid residue was added saturated aqueous solution of $NaHCO_3$ (10 mL). Upon cooling to 0 °C, the precipitate was filtered, washed with ice-cold water, light petrol, cold ether (3×10 mL), dried, washed with cold EtOH (3×10 mL), and dried to give **3** (3.318 g, 98%) as almost white (when starting pyrimidinone **7** was treated with MeCN as described below) or slightly cream-coloured powder. Mp 261.5 °C (decomp., butan-1-ol). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.35 (1H, d, $^4J_{N(1)H,N(3)H}$=1.8 Hz, $N_{(1)}H$), 7.47 (1H, dd, $^3J_{N(3)H,4\text{-}H}$=3.8, $^4J_{N(3)H,N(1)H}$=1.8 Hz, $N_{(3)}H$), 7.16–7.45 (9H, m, CH in Ph and C_6H_4), 5.14 (1H, t, $^3J_{OH,CH2}$=5.7 Hz, OH), 4.07 (1H, ddd, $^3J_{4\text{-}H,CH(A)}$=6.4, $^3J_{4\text{-}H,N(3)H}$=3.8, $^3J_{4\text{-}H,CH(B)}$=3.1 Hz, 4-H), 3.54 (1H, ddd, $^2J_{CH(A),CH(B)}$=10.9, $^3J_{CH(A),4\text{-}H}$=6.4, $^3J_{CH(A),OH}$=5.7 Hz, CH(A) in OCH_2), 3.49 (1H, ddd, $^2J_{CH(B),CH(A)}$=10.9, $^3J_{CH(B),OH}$=5.7, $^3J_{CH(B),4\text{-}H}$=3.1 Hz, CH(B) in OCH_2), 2.34 (3H, s, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 152.3 ($C_{(2)}$), 150.3 ($C_{(6)}$), 143.0 ($C_{(4)}$ in 4-MeC_6H_4), 139.7 ($C_{(1)}$ in 4-MeC_6H_4), 132.3 ($C_{(1)}$ in Ph), 129.6 ($C_{(4)}$ in Ph), 129.5 (br, $C_{(2)}$ and $C_{(6)}$ in Ph), 129.4 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 127.4 ($C_{(3)}$ and $C_{(5)}$ in Ph), 126.5 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 106.2 ($C_{(5)}$), 64.7 (OCH_2), 53.5 ($C_{(4)}$), 21.0 (CH_3 in Ts). IR (Nujol) ν, cm^{-1}: 3349s, 3268m, 3212s, 3096s (ν NH, ν OH), 3060w, 3043w, 3023w (ν CH_{arom}), 1681vs, 1671vs (amide-I), 1652vs (ν C=C), 1600m (ν CC_{arom}), 1308s (ν_{as} SO_2), 1145vs (ν_s SO_2), 807m (δ CH_{arom} in Ts), 769s, 701s (δ CH in Ph). Anal. Calcd for $C_{18}H_{18}N_2O_4S$: C, 60.32; H, 5.06; N, 7.82. Found: C, 60.43; H, 5.14; N, 7.71.

*4.1.2. N-[(1-Benzoyloxy-4-oxo-4-phenyl-3-tosyl)but-2-yl]urea (**6**).* To a mixture of tosylacetophenone (**5**) (2.298 g, 8.38 mmol) and NaH (0.201 g, 8.38 mmol) was added dry MeCN (16.2 mL), and the obtained mixture was stirred for 10 min upon cooling on ice-bath. Then to the resulting dense enolate suspension were added sulfone **4**[4] (3.028 g, 8.36 mmol) and MeCN (4.6 mL). The formed suspension was stirred at rt for 8 h 16 min, and the solvent was removed in vacuum. To the white solid residue was added a saturated aqueous solution of $NaHCO_3$ (12 mL). The obtained mixture was left for 4 h in a water bath (40 °C) and then overnight at rt. Upon cooling to 0 °C, the precipitate was filtered, washed with ice-cold water, light petrol, dried, washed with cold (−10 °C) ether, and dried to give **6** (3.838 g, 96%) as a mixture of two diastereomers, 59:41. After crystallization from ethyl acetate the diastereomeric ratio changed to 58:42. Mp 184.5–185 °C (decomp., ethyl acetate). ^{1}H NMR of the major diastereomer (300.13 MHz, DMSO-d_6) δ: 6.34 (1H, d, $^3J_{NH,CH}$=9.1 Hz, NH), 6.06 (1H, d, $^3J_{CH-S,CH}$=5.7 Hz, CH–SO_2), 5.77 (2H, s, NH_2), 4.89 (1H, dddd, $^3J_{CH,NH}$=9.1, $^3J_{CH,CH-S}$=5.7, $^3J_{CH,CH(A)}$=4.8, $^3J_{CH,CH(B)}$=4.2 Hz, CH–N), 4.43 (1H, dd, $^2J_{CH(A),CH(B)}$=11.3, $^3J_{CH(A),CH}$=4.8 Hz, CH(A) in OCH_2), 4.40 (1H, dd, $^2J_{CH(B),CH(A)}$=11.3, $^3J_{CH(B),CH}$=4.2 Hz, CH(B) in OCH_2), 2.33 (3H, s, CH_3). ^{1}H NMR of the minor diastereomer (300.13 MHz, DMSO-d_6) δ: 6.32 (1H, d, $^3J_{NH,CH}$=8.6 Hz, NH), 6.04 (1H, d, $^3J_{CH-S,CH}$=8.4 Hz, CH–SO_2), 5.74 (2H, s, NH_2), 4.66 (1H, dddd, $^3J_{CH,NH}$=8.6, $^3J_{CH,CH-S}$=8.4, $^3J_{CH,CH(B)}$=6.0, $^3J_{CH,CH(A)}$=4.1 Hz, CH–N), 4.39 (1H, dd, $^2J_{CH(A),CH(B)}$=11.4, $^3J_{CH(A),CH}$=4.1 Hz, CH(A) in OCH_2), 4.20 (1H, dd, $^2J_{CH(B),CH(A)}$=11.4, $^3J_{CH(B),CH}$=6.0 Hz, CH(B) in OCH_2), 2.37 (3H, s, CH_3). Signals of aromatic protons of PhCOO, Ph and Ts for both diastereomers lie at 7.31–7.97 ppm (12H). ^{13}C NMR of the major diastereomer (75.48 MHz, DMSO-d_6) δ: 192.34 (C=O in COPh), 165.24 (C=O in PhCOO), 157.58 (N–C=O), 145.08 ($C_{(4)}$ in 4-MeC_6H_4), 136.61 ($C_{(1)}$ in COPh), 134.74 ($C_{(1)}$ in 4-MeC_6H_4), 134.12 ($C_{(4)}$ in COPh), 133.34 ($C_{(4)}$ in PhCOO), 129.55 ($C_{(2)}$ and $C_{(6)}$ in PhCOO), 129.22 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 129.17, 128.90, 128.63 ($C_{(3)}$ and $C_{(5)}$ in PhCOO, $C_{(2)}$, $C_{(3)}$, $C_{(5)}$ and $C_{(6)}$ in COPh), 129.03 ($C_{(1)}$ in PhCOO), 128.43 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 67.65 (CH–SO_2), 66.04 (OCH_2), 48.35 (CH–N), 21.10 (CH_3). ^{13}C NMR of the minor diastereomer (75.48 MHz, DMSO-d_6) δ: 191.81 (C=O in COPh), 165.17 (C=O in PhCOO), 157.56 (N–C=O), 145.05 ($C_{(4)}$ in 4-MeC_6H_4), 136.57 ($C_{(1)}$ in COPh), 135.03 ($C_{(1)}$ in 4-MeC_6H_4), 134.22 ($C_{(4)}$ in COPh), 133.39 ($C_{(4)}$ in PhCOO), 129.60 ($C_{(2)}$ and $C_{(6)}$ in PhCOO), 129.26 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 129.20, 128.79, 128.78 ($C_{(3)}$ and $C_{(5)}$ in PhCOO, $C_{(2)}$, $C_{(3)}$, $C_{(5)}$ and $C_{(6)}$ in COPh), 129.00 ($C_{(1)}$ in PhCOO), 128.47 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 68.95 (CH–SO_2), 65.12 (OCH_2), 48.76 (CH–N), 21.14 (CH_3). IR (Nujol) ν, cm^{-1}: 3447s, 3414s, 3361m, 3309m, 3241m, 3156s (ν NH), 3056m, 3033w (ν CH_{arom}), 1725s (C=O in PhCOO), 1689s, 1680s (C=O in COPh and amide-I), 1595s (ν CC_{arom}), 1537s (amide-II), 1493m (ν CC_{arom}), 1312s (ν_{as} SO_2), 1284s (ν C–O), 1129s (ν_s SO_2), 1114s, 1080s (ν C–O), 814s (δ CH_{arom} in Ts), 758s, 707s (δ CH in Ph). Anal. Calcd for $C_{25}H_{24}N_2O_6S$: C, 62.49; H, 5.03; N, 5.83. Found: C, 62.51; H, 5.11; N, 5.76.

*4.1.3. 4-(Benzoyloxymethyl)-6-phenyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one (**7**).* A solution of compound **6** (5.083 g, 10.58 mmol) and TsOH·H_2O (6.029 g, 31.69 mmol) in MeCN (50 mL) was refluxed for 20 h under stirring and then solvent was removed in vacuum. To the black, oily residue was added a saturated aqueous solution of $NaHCO_3$ (30 mL), and the resulting mixture was neutralized by addition of solid $NaHCO_3$ to pH 8. The obtained suspension was left at rt for 2 h. Upon cooling to 0 °C, the precipitate was filtered, washed thoroughly with ice-cold water, light petrol, cold (−10 °C) ether, and dried to give **7** (3.546 g, 73%). If **7** is supposed to be used for preparation of mesyloxymethyl derivative **9**, then it is useful to boil it with MeCN, cool to −10 °C, filter off and wash three times with cold MeCN. When 8.682 g of **7** was treated as described with MeCN (30 mL, 3×5 mL for washing), 8.400 g was obtained. After this procedure, the substance becomes cream-coloured instead of brown. For preparation of chloromethyl derivative **10** treatment of **7** with MeCN is not necessary. Mp 257.5–258 °C (decomp., MeCN). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.72 (1H, d, $^4J_{N(1)H,N(3)H}$=1.8 Hz, $N_{(1)}H$), 7.81 (1H, dd, $^3J_{N(3)H,4\text{-}H}$=3.7, $^4J_{N(3)H,N(1)H}$=1.8 Hz, $N_{(3)}H$), 8.02–8.07 (2H, m, $C_{(2)}H$ and $C_{(6)}H$ in PhCOO), 7.64–7.70 (1H, m, $C_{(4)}H$ in PhCOO), 7.48–7.55 (2H, m, $C_{(3)}H$ and $C_{(5)}H$ in PhCOO), 7.39–7.46 (1H, m, $C_{(4)}H$ in 7-Ph), 7.28–7.35 (4H, m, $C_{(3)}H$ and $C_{(5)}H$ in 7-Ph, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.21–7.26 (2H, m, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 7.11–7.16 (2H, m, $C_{(2)}H$ and $C_{(6)}H$ in 7-Ph), 4.55 (1H, ddd, $^3J_{4\text{-}H,CH(A)}$=5.0, $^3J_{4\text{-}H,N(3)H}$=3.7, $^3J_{4\text{-}H,CH(B)}$=3.2 Hz, 4-H), 4.51 (1H, dd, $^2J_{CH(A),CH(B)}$=11.2, $^3J_{CH(A),4\text{-}H}$=5.0 Hz, CH(A) in OCH_2), 4.34 (1H, dd, $^2J_{CH(B),CH(A)}$=11.2, $^3J_{CH(B),4\text{-}H}$=3.2 Hz, CH(B) in OCH_2), 2.33 (3H, s, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 165.7 (C=O in PhCOO), 152.1 ($C_{(2)}$), 150.9 ($C_{(6)}$), 143.3 ($C_{(4)}$ in 4-MeC_6H_4), 139.3 ($C_{(1)}$ in 4-

MeC_6H_4), 133.5 ($C_{(4)}$ in PhCOO), 131.9 ($C_{(1)}$ in 6-Ph), 129.7 ($C_{(4)}$ in 6-Ph), 129.51 ($C_{(2)}$ and $C_{(6)}$ in PhCOO), 129.47 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 129.3 ($C_{(1)}$ in PhCOO), 129.2 (br, $C_{(2)}$ and $C_{(6)}$ in 6-Ph), 128.8 ($C_{(3)}$ and $C_{(5)}$ in PhCOO), 127.5 ($C_{(3)}$ and $C_{(5)}$ in 6-Ph), 126.6 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 105.4 ($C_{(5)}$), 67.8 (OCH_2), 50.5 ($C_{(4)}$), 21.0 (CH_3). IR (Nujol) ν, cm^{-1}: 3318s, 3208sh, 3199s, 3089s (ν NH), 3024w (ν CH_{arom}), 1699vs (ν C=O in PhCOO and amide-I), 1651s (ν C=C), 1600m, 1492w (ν CC_{arom}), 1286s (ν_{as} SO_2), 1146s (ν_s SO_2), 1128s (ν C–O), 809m (δ CH_{arom} in Ts), 758m, 715s (δ CH in Ph). Anal. Calcd for $C_{25}H_{22}N_2O_5S$: C, 64.92; H, 4.79; N, 6.06. Found: C, 64.75; H, 4.76; N, 6.12.

*4.1.4. 4-(Mesyloxymethyl)-6-phenyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one (**9**).* To a stirred suspension of hydroxymethylpyrimidine **3** (1.627 g, 4.54 mmol) and DMAP (1.719 g, 14.07 mmol) in dry CH_2Cl_2 (13.4 mL) at 0 °C was added a solution of MsCl (1.058 g, 9.24 mmol) in dry CH_2Cl_2 (6.6 mL) over 4 min. The obtained suspension was refluxed under stirring for 45 min. The formed deep-brown solution was concentrated under vacuum to give a stable foam. Ice-cold water (20 mL) was added to the foam and the resulting oily substance was triturated under cooling until complete crystallization. The precipitate was filtered, washed with ice-cold water, hexane, ether (3×5 mL) and recrystallized from EtOH to give **9** (1.427 g, 72%) as a yellowish solid, which was used for the diazepine synthesis. An analytical sample was obtained as a white solid by crystallization of the crude **9** from MeCN. Mp 116–119 °C (decomp., MeCN). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.66 (1H, d, $^4J_{N(1)H,N(3)H}$=1.9 Hz, $N_{(1)}H$), 7.82 (1H, dd, $^3J_{N(3)H,4\text{-}H}$=3.9, $^4J_{N(3)H,N(1)H}$=1.9 Hz, $N_{(3)}H$), 7.41–7.48 (1H, m, CH_{para} in Ph), 7.32–7.38 (2H, m, CH_{meta} in Ph), 7.29–7.33 (2H, m, AA′ part of AA′XX′ spin system, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.23–7.28 (2H, m, XX′ part of AA′XX′ spin system, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 7.17–7.23 (2H, m, CH_{ortho} in Ph), 4.44 (1H, ddd, $^3J_{4\text{-}H,CH(A)}$=5.9, $^3J_{4\text{-}H,N(3)H}$=3.9, $^3J_{4\text{-}H,CH(B)}$=2.9 Hz, 4-H), 4.35 (1H, dd, $^2J_{CH(A),CH(B)}$=10.3, $^3J_{CH(A),4\text{-}H}$=5.9 Hz, H(A) in CH_2O), 4.24 (1H, dd, $^2J_{CH(B),CH(A)}$=10.3, $^3J_{CH(B),4\text{-}H}$=2.9 Hz, H(B) in CH_2O), 3.24 (3H, s, CH_3SO_2), 2.34 (3H, s, CH_3 in Ts). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 151.6 ($C_{(2)}$), 151.5 ($C_{(6)}$), 143.4 ($C_{(4)}$ in 4-MeC_6H_4), 139.1 ($C_{(1)}$ in 4-MeC_6H_4), 131.7 ($C_{(1)}$ in Ph), 129.8 ($C_{(4)}$ in Ph), 129.5 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 129.3 (br, $C_{(2)}$ and $C_{(6)}$ in Ph), 127.5 ($C_{(3)}$ and $C_{(5)}$ in Ph), 126.6 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 104.1 ($C_{(5)}$), 72.3 (OCH_2), 50.5 ($C_{(4)}$), 36.9 (CH_3 in Ms), 21.0 (CH_3 in Ts). IR (Nujol) ν, cm^{-1}: 3200s, 3085sh, 3065s (ν NH), 1710s (amide-I), 1618s (ν C=C), 1599m, 1495m (ν CC_{arom}), 1360s (ν_{as} SO_2 in OMs), 1315m (ν_{as} SO_2 in Ts), 1176s (ν_s SO_2 in OMs), 1149s (ν_s SO_2 in Ts), 814m (δ CH_{arom} in Ts), 765m, 701m (δ CH in Ph). Anal. Calcd for $C_{19}H_{20}N_2O_6S_2$: C, 52.28; H, 4.62; N, 6.42. Found: C, 52.21; H, 4.68; N, 6.68.

*4.1.5. 4-(Chloromethyl)-6-phenyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one (**10**).* To a mixture of hydroxymethylpyrimidine **3** (2.151 g, 6.00 mmol) and PPh_3 (1.964 g, 7.49 mmol) were added dry MeCN (17 mL) and CCl_4 (1.14 mL, 11.82 mmol). The obtained suspension was refluxed under stirring for 23 min. In 2 min after reflux solid substance dissolved and after additional 2 min new precipitate occurred. After the reaction was complete, the formed suspension was cooled to −10 °C, the precipitate was filtered, washed with MeCN (4×6 mL) and dried to give **10** (2.031 g, 90%) as slightly yellowish powder. The colour remained the same after crystallization from *n*-BuOH with charcoal. Mp 243.5 °C (decomp., butan-1-ol). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.61 (1H, d, $^4J_{N(1)H,N(3)H}$=1.9 Hz, $N_{(1)}H$), 7.77 (1H, dd, $^3J_{N(3)H,4\text{-}H}$=3.7, $^4J_{N(3)H,N(1)H}$=1.9 Hz, $N_{(3)}H$), 7.40–7.46 (1H, m, CH_{para} in Ph), 7.30–7.36 (2H, m, CH_{meta} in Ph), 7.26–7.30 (2H, m, AA′ part of AA′XX′ spin system, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.21–7.26 (2H, m, XX′ part of AA′XX′ spin system, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 7.13–7.19 (2H, m, CH_{ortho} in Ph), 4.50 (1H, ddd, $^3J_{4\text{-}H,CH(A)}$=5.1, $^3J_{4\text{-}H,N(3)H}$=3.7, $^3J_{4\text{-}H,CH(B)}$=2.8 Hz, 4-H), 3.89 (1H, dd, $^2J_{CH(A),CH(B)}$=11.4, $^3J_{4\text{-}H,CH(A)}$=5.1 Hz, H(A) in CH_2), 3.76 (1H, dd, $^2J_{CH(B),CH(A)}$=11.4, $^3J_{CH(B),4\text{-}H}$=2.8 Hz, H(B) in CH_2), 2.34 (3H, s, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 151.6 ($C_{(2)}$), 151.2 ($C_{(6)}$), 143.3 ($C_{(4)}$ in 4-MeC_6H_4), 139.1 ($C_{(1)}$ in 4-MeC_6H_4), 131.8 ($C_{(1)}$ in Ph), 129.8 ($C_{(4)}$ in Ph), 129.5 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 129.3 (br, $C_{(2)}$ and $C_{(6)}$ in Ph), 127.5 ($C_{(3)}$ and $C_{(5)}$ in Ph), 126.6 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 105.4 ($C_{(5)}$), 52.4 ($C_{(4)}$), 51.0 (CH_2Cl), 21.0 (CH_3 in Ts). IR (Nujol) ν, cm^{-1}: 3256s, 3135m (ν NH), 3060w, 3045w, 3029w (ν CH_{arom}), 1700vs (amide-I), 1629s (ν C=C), 1596m, 1493w (ν CC_{arom}), 1304s (ν_{as} SO_2), 1140s (ν_s SO_2), 820m (δ CH_{arom} in Ts), 765s, 693s (δ CH in Ph). Anal. Calcd for $C_{18}H_{17}ClN_2O_3S$: C, 57.37; H, 4.55; N, 7.43. Found: C, 57.41; H, 4.51; N, 7.28.

*4.1.6. 4-(Chloromethyl)-6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one (**11**).* To a mixture of hydroxymethylpyrimidine **8** (0.374 g, 1.26 mmol) and PPh_3 (0.415 g, 1.58 mmol) were added dry MeCN (6 mL) and CCl_4 (0.25 mL, 2.59 mmol). The obtained suspension was refluxed under stirring for 30 min. After the reaction was complete, the formed solution was cooled, solvent was removed under vacuum, and the residue was purified by column chromatography on silica gel (43.3 g) using $CHCl_3$/light petrol (1:2 to 5:1), $CHCl_3$, $CHCl_3$/MeOH (100:1 to 40:1) as eluents to give **11** (0.237 g, 60%). Mp 193–193.5 °C (decomp., ethyl acetate). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.44 (1H, d, $^4J_{N(1)H,N(3)H}$=1.9 Hz, $N_{(1)}H$), 7.73–7.77 (2H, m, AA′ part of AA′XX′ spin system, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.64 (1H, dd, $^3J_{N(3)H,4\text{-}H}$=3.6, $^4J_{N(3)H,N(1)H}$=1.9 Hz, $N_{(3)}H$), 7.40–7.45 (2H, m, XX′ part of AA′XX′ spin system, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 4.29 (1H, ddd, $^3J_{4\text{-}H,CH(A)}$=5.5, $^3J_{4\text{-}H,N(3)H}$=3.6, $^3J_{4\text{-}H,CH(B)}$=2.8 Hz, 4-H), 3.72 (1H, dd, $^2J_{CH(A),C(H)B}$=11.3, $^3J_{CH(A),4\text{-}H}$=5.5 Hz, H(A) in CH_2), 3.63 (1H, dd, $^2J_{CH(B),CH(A)}$=11.3, $^3J_{CH(B),4\text{-}H}$=2.8 Hz, H(B) in CH_2), 2.39 (3H, s, CH_3 in Ts), 2.17 (3H, s, 6-CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 151.8 ($C_{(2)}$), 149.8 ($C_{(6)}$), 143.6 ($C_{(4)}$ in 4-MeC_6H_4), 139.8 ($C_{(1)}$ in 4-MeC_6H_4), 129.9 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 126.2 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 103.3 ($C_{(5)}$), 52.3 ($C_{(4)}$), 50.6 (CH_2Cl), 20.9 (CH_3 in Ts), 16.6 (6-CH_3). IR (Nujol) ν, cm^{-1}: 3225s, 3097s (ν NH), 3033w (ν CH_{arom}), 1719s (amide-I), 1646s (ν C=C), 1597m (ν CC_{arom}), 1301s (ν_{as} SO_2), 1150s (ν_s SO_2), 810m (δ CH_{arom}). Anal. Calcd for $C_{13}H_{15}ClN_2O_3S$: C, 49.60; H, 4.80; N, 8.90. Found: C, 49.75; H, 4.93; N, 8.90.

*4.1.7. 4-[Di(ethoxycarbonyl)methyl]-7-phenyl-6-tosyl-2,3,4,5-tetrahydro-1H-1,3-diazepin-2-one (**15**).* To a stirred suspension of NaH (0.017 g, 0.71 mmol) in dry MeCN (1 mL) was added a solution of diethyl malonate (0.124 g, 0.77 mmol) in dry MeCN (1.5 mL). The obtained white suspension was stirred for 10 min, then mesyloxymethylpyrimidine **9** (0.243 g, 0.56 mmol) and MeCN (1.5 mL) were added. The reaction mixture was stirred at rt for 3 h 53 min, the solvent was removed under vacuum and the residue was triturated with light petrol (3 mL) and H_2O (3 mL) until crystallization. The obtained suspension was cooled, the precipitate was filtered, washed with ice-cold water, light petrol, and dried to give **15** (0.253 g, 91%). In a similar manner, compound **15** (0.119 g, 80%) was prepared from chloromethylpyrimidine **10** (0.112 g, 0.30 mmol), diethyl malonate (0.069 g, 0.43 mmol) and NaH (0.009 g, 0.38 mmol) in MeCN (3.6 mL) (rt, 4 h 38 min). Mp 163.5–164.5 °C (ethyl acetate). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.57 (1H, d, $^4J_{N(1)H,N(3)H}$=1.8 Hz, $N_{(1)}H$), 7.55 (1H, dd, $^3J_{N(3)H,4\text{-}H}$=5.1, $^4J_{N(3)H,N(1)H}$=1.8 Hz, $N_{(3)}H$), 7.26–7.41 (7H, m, CH_{arom} in Ph, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.07–7.13 (2H, m, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 4.05–4.22 (4H, m, two OCH_2), 3.93 (1H, dddd, $^3J_{4\text{-}H,CH}$=8.8, $^3J_{4\text{-}H,5\text{-}H(A)}$=7.3, $^3J_{4\text{-}H,N(3)H}$=5.1, $^3J_{4\text{-}H,5\text{-}H(B)}$=2.4 Hz, 4-H), 3.73 (1H, d, $^3J_{CH,4\text{-}H}$=8.8 Hz, CH in $CH(COOEt)_2$), 3.03 (1H, dd, $^2J_{5\text{-}H(A),5\text{-}H(B)}$=15.8, $^3J_{5\text{-}H(A),4\text{-}H}$=7.3 Hz, 5-H(A)), 2.77 (1H, dd, $^2J_{5\text{-}H(B),5\text{-}H(A)}$=15.8, $^3J_{5\text{-}H(B),4\text{-}H}$=2.4 Hz, 5-H(B)), 2.36 (3H, s, CH_3 in Ts), 1.19 (6H, t, $^3J_{CH3,CH2}$=7.1 Hz, two CH_3 in $CH(COOEt)_2$). ^{13}C NMR (75.48 MHz,

DMSO-d_6) δ: 166.7, 166.5 (C=O in CH(COOEt)$_2$), 154.1 ($C_{(2)}$), 147.8 ($C_{(7)}$), 143.1 ($C_{(4)}$ in 4-MeC_6H_4), 139.1 ($C_{(1)}$ in 4-MeC_6H_4), 135.2 ($C_{(1)}$ in Ph), 129.5 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 129.2 (br, $C_{(2)}$ and $C_{(6)}$ in Ph), 129.0 ($C_{(4)}$ in Ph), 127.4 ($C_{(3)}$ and $C_{(5)}$ in Ph), 126.7 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 115.1 ($C_{(6)}$), 61.6, 61.4 (OCH_2 in CH(COOEt)$_2$), 55.3 (CH in CH(COOEt)$_2$), 50.9 ($C_{(4)}$), 31.5 ($C_{(5)}$), 21.0 (CH_3 in Ts), 13.84, 13.82 (CH_3 in CH(COOEt)$_2$). IR (Nujol) ν, cm^{-1}: 3249s, 3149m, 3112s (ν NH), 3022w (ν CH_{arom}), 1756s, 1727m (ν C=O in COOEt), 1695s (amide-I), 1629s (ν C=C), 1598m, 1492m (ν CC_{arom}), 1307s (ν_{as} SO_2), 1242m (ν C–O), 1148s (ν_s SO_2), 1088s (ν C–O), 818m (δ CH_{arom} in Ts), 754m, 691m (δ CH in Ph). Anal. Calcd for $C_{25}H_{28}N_2O_7S$: C, 59.99; H, 5.64; N, 5.60. Found: C, 59.67; H, 5.84; N, 5.57.

*4.1.8. 7-Phenyl-4-phenylthio-6-tosyl-2,3,4,5-tetrahydro-1H-1,3-diazepin-2-one (**16**).* To a stirred suspension of NaH (0.011 g, 0.46 mmol) in MeCN (1 mL) was added a solution of thiophenol (0.053 g, 0.48 mmol) in MeCN (1.5 mL), and the resulting white suspension was stirred at rt for 10 min. Mesyloxymethylpyrimidine **9** (0.180 g, 0.41 mmol) and MeCN (0.5 mL) were added and the obtained suspension was stirred at rt for 4 h. After the reaction was complete the solvent was removed under vacuum, the oily residue was triturated with light petrol (3 mL) and H_2O (2 mL) under cooling until complete crystallization. The formed suspension was cooled, the precipitate was filtered, washed with ice-cold water, light petrol, and dried to give crude **16** (0.173 g). In a similar manner and in the same purity, compound **16** (0.880 g) was also prepared from chloromethylpyrimidine **10** (0.765 g, 2.03 mmol), PhSH (0.349 g, 3.17 mmol) and NaH (0.073 g, 3.04 mmol) in MeCN (10 mL) (rt, 5 h). Crude product (0.310 g) was purified by column chromatography on silica gel (15.1 g) using $CHCl_3$/light petrol (1:2 to 70:30) as eluent to give pure **16** in 65% overall yield (0.210 g). Mp 92.5–93.5 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.67 (1H, d, $^4J_{N(1)H,N(3)H}$=2.0 Hz, $N_{(1)}$H), 8.18 (1H, dd, $^3J_{N(3)H,4-H}$=5.2, $^4J_{N(3)H,N(1)H}$=2.0 Hz, $N_{(3)}$H), 7.20–7.50 (12H, m, CH_{arom} in Ph and SPh, $C_{(2)}$H and $C_{(6)}$H in 4-MeC_6H_4), 7.06–7.11 (2H, m, $C_{(3)}$H and $C_{(5)}$H in 4-MeC_6H_4), 4.90 (1H, ddd, $^3J_{4-H,5-H(A)}$=7.0, $^3J_{4-H,N(3)H}$=5.2, $^3J_{4-H,5-H(B)}$=2.7 Hz, 4-H), 3.33 (1H, dd, $^2J_{5-H(A),5-H(B)}$=15.9, $^3J_{5-H(A),4-H}$=7.0 Hz, 5-H(A)), 3.02 (1H, dd, $^2J_{5-H(B),5-H(A)}$=15.9, $^3J_{5-H(B),4-H}$=2.7 Hz, 5-H(B)), 2.34 (3H, s, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 153.7 ($C_{(2)}$), 147.6 ($C_{(7)}$), 143.0 ($C_{(4)}$ in 4-MeC_6H_4), 139.1 ($C_{(1)}$ in 4-MeC_6H_4), 135.1 ($C_{(1)}$ in Ph), 133.0 ($C_{(1)}$ in SPh), 132.2 ($C_{(2)}$ and $C_{(6)}$ in SPh), 129.34 (br, $C_{(2)}$ and $C_{(6)}$ in Ph), 129.25 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 129.1 ($C_{(3)}$ and $C_{(5)}$ in SPh), 129.0 ($C_{(4)}$ in Ph), 127.6 ($C_{(4)}$ in SPh), 127.4 ($C_{(3)}$ and $C_{(5)}$ in Ph), 127.0 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 115.7 ($C_{(6)}$), 59.6 ($C_{(4)}$), 35.5 ($C_{(5)}$), 21.0 (CH_3 in Ts). IR (Nujol) ν, cm^{-1}: 3214s, 3201s, 3056s (ν NH), 1685s (amide-I), 1627s (ν C=C), 1597m, 1492m (ν CC_{arom}), 1300s (ν_{as} SO_2), 1143s (ν_s SO_2), 813m (δ CH_{arom} in Ts), 748s, 696s (δ CH in Ph and SPh). Anal. Calcd for $C_{24}H_{22}N_2O_3S_2$: C, 63.98; H, 4.92; N, 6.22. Found: C, 63.82; H, 5.06; N, 6.51.

*4.1.9. 4-Cyano-7-phenyl-6-tosyl-2,3,4,5-tetrahydro-1H-1,3-diazepin-2-one (**17**).* To a mixture of mesyloxymethylpyrimidine **9** (0.508 g, 1.16 mmol) and finely powdered NaCN (0.074 g, 1.51 mmol) was added dry DMF (1 mL). The obtained suspension was stirred at rt for 1 h 32 min, then ice-cold water (10 mL) was added and the solid residue was triturated until complete crystallization. Upon cooling to 0 °C, the precipitate was filtered, washed with ice-cold water, light petrol, ether/light petrol mixture (1:1 v/v, 2×3 mL), and dried to give crude **17** (0.401 g). Crude product (0.332 g) was purified by column chromatography on silica gel (16.7 g) using $CHCl_3$/MeOH (60:1) as eluent to give pure **17** in 65% overall yield (0.231 g). Mp 224.5–225 oC (decomp., ethanol). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.86 (1H, d, $^4J_{N(1)H,N(3)H}$=1.9 Hz, $N_{(1)}$H), 8.28 (1H, dd, $^3J_{N(3)H,4-H}$=6.7, $^4J_{N(3)H,N(1)H}$=1.9 Hz, $N_{(3)}$H), 7.31–7.37 (1H, m, CH_{para} in Ph), 7.18–7.29 (6H, m, CH_{meta} in Ph and CH_{arom} in Ts), 6.95–7.04 (2H, m, CH_{ortho} in Ph), 4.87 (1H, ddd, $^3J_{4-H,N(3)H}$=6.7, $^3J_{4-H,5-H(A)}$=5.7, $^3J_{4-H,5-H(B)}$=2.7 Hz, 4-H), 3.47 (1H, dd, $^2J_{5-H(A),5-H(B)}$=16.6, $^3J_{5-H(A),4-H}$=5.7 Hz, 5-H(A)), 2.92 (1H, dd, $^2J_{5-H(B),5-H(A)}$=16.6, $^3J_{5-H(B),4-H}$=2.7 Hz, 5-H(B)), 2.34 (3H, s, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 153.7 ($C_{(2)}$), 147.8 ($C_{(7)}$), 143.0 ($C_{(4)}$ in 4-MeC_6H_4), 139.1 ($C_{(1)}$ in 4-MeC_6H_4), 134.8 ($C_{(1)}$ in Ph), 129.3 ($C_{(2)}$ and $C_{(6)}$ in Ph), 129.2 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 129.0 ($C_{(4)}$ in Ph), 127.4 ($C_{(3)}$ and $C_{(5)}$ in Ph), 126.9 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 118.1 (CN), 115.4 ($C_{(6)}$), 42.1 ($C_{(4)}$), 32.4 ($C_{(5)}$), 21.0 (CH_3). IR (Nujol) ν, cm^{-1}: 3379s, 3278s, 3155m (ν NH), 3049w, 3029w (ν CH_{arom}), 2240vw (ν CN), 1688s (amide-I), 1635s (ν C=C), 1598m, 1492m (ν CC_{arom}), 1279s (ν_{as} SO_2), 1143s (ν_s SO_2), 811m (δ CH_{arom} in Ts), 758m, 698m (δ CH in Ph). Anal. Calcd for $C_{19}H_{17}N_3O_3S$: C, 62.11; H, 4.66; N, 11.44. Found: C, 62.33; H, 5.00; N, 11.44.

*4.1.10. 7-Phenyl-4-phthalimido-6-tosyl-2,3,4,5-tetrahydro-1H-1,3-diazepin-2-one (**18**).* To a mixture of mesyloxymethylpyrimidine **9** (0.514 g, 1.18 mmol) and potassium phthalimide (0.320 g, 1.73 mmol) was added MeCN (10 mL) and the obtained suspension was refluxed under stirring for 15 min. In 1 min after the beginning of the reaction, the solid substance dissolved and after additional 2 min new precipitate occurred. After the reaction was complete, the solvent was removed under vacuum, to the solid residue was added H_2O (5 mL) and the resulting mixture was triturated until complete crystallization. The formed suspension was cooled to 0 °C, the precipitate was filtered, washed with ice-cold water, light petrol, and dried to give **18** (0.528 g, 92%). Mp 250.5 °C (decomp., DMF/ethanol, 1:1 v/v). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.92 (1H, d, $^4J_{N(1)H,N(3)H}$=1.9 Hz, $N_{(1)}$H), 7.83–7.92 (4H, m, CH in phthalimido group), 7.53 (1H, ddd, $^4J_{N(3)H,N(1)H}$=$^3J_{N(3)H,4-H}$=1.9, $^4J_{N(3)H,5-H(B)}$=1.1 Hz, $N_{(3)}$H), 7.34–7.48 (5H, m, $C_{(2)}$H and $C_{(6)}$H in 4-MeC_6H_4, $C_{(3)}$H, $C_{(4)}$H and $C_{(5)}$H in Ph), 7.22–7.29 (4H, m, $C_{(3)}$H and $C_{(5)}$H in 4-MeC_6H_4, $C_{(2)}$H and $C_{(6)}$H in Ph), 5.28 (1H, ddd, $^3J_{4-H,5-H(A)}$=9.9, $^3J_{4-H,5-H(B)}$=3.2, $^3J_{4-H,N(3)H}$=1.9 Hz, 4-H), 3.48 (1H, dd, $^2J_{5-H(A),5-H(B)}$=14.6, $^3J_{5-H(A),4-H}$=9.9 Hz, 5-H(A)), 3.09 (1H, ddd, $^2J_{5-H(B),5-H(A)}$=14.6, $^3J_{5-H(B),4-H}$=3.2, $^3J_{5-H(B),N(3)H}$=1.1 Hz, 5-H(B)), 2.31 (3H, s, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 166.9 (C=O in phthalimido group), 153.7 ($C_{(2)}$), 149.4 ($C_{(7)}$), 143.5 ($C_{(4)}$ in 4-MeC_6H_4), 138.4 ($C_{(1)}$ in 4-MeC_6H_4), 134.9 ($C_{(1)}$ in Ph), 134.6 ($C_{(4)}$ and $C_{(5)}$ in phthalimido group), 131.5 ($C_{(1)}$ and $C_{(2)}$ in phthalimido group), 129.7 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4, $C_{(2)}$, $C_{(6)}$ and $C_{(4)}$ in Ph), 127.5 ($C_{(3)}$ and $C_{(5)}$ in Ph), 127.0 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 123.2 ($C_{(3)}$ and $C_{(6)}$ in phthalimido group), 116.6 ($C_{(6)}$), 61.5 ($C_{(4)}$), 30.7 ($C_{(5)}$), 21.1 (CH_3). IR (Nujol) ν, cm^{-1}: 3316s, 3216m, 3178m, 3126m, 3095m (ν NH), 3074w, 3062w (ν CH_{arom}), 1778m, 1724vs (amide-I in phthalimido group), 1688s (amide-I in diazepinone moiety), 1625s (ν C=C), 1596m, 1505m, 1494w (ν CC_{arom}), 1321s (ν_{as} SO_2), 1146s (ν_s SO_2), 810s (δ CH_{arom} in Ts), 772m (δ CH in Ph), 725s (δ CH in phthalimido group), 696s (δ CH in Ph). Anal. Calcd for $C_{26}H_{21}N_3O_5S$: C, 64.05; H, 4.34; N, 8.62. Found: C, 64.12; H, 4.52; N, 8.61.

*4.1.11. 7-Methyl-4-phthalimido-6-tosyl-2,3,4,5-tetrahydro-1H-1,3-diazepin-2-one (**19**).* Compound **19** was prepared (analogously to **18**) from mesyloxymethylpyrimidine **14** (0.350 g, 0.93 mmol) and potassium phthalimide (0.253 g, 1.37 mmol) in MeCN (5 mL, reflux, 15 min) (0.369 g, 93%) or from chloromethylpyrimidine **11** (0.057 g, 0.18 mmol) and potassium phthalimide (0.051 g, 0.28 mmol) in MeCN (1 mL, reflux, 53 min) (0.065 g, 84%). Mp 240.5 °C (decomp., DMF/ethanol, 1:2 v/v). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.88 (1H, d, $^4J_{N(1)H,N(3)H}$=1.8 Hz, $N_{(1)}$H), 7.80–7.88 (4H, m, CH in phthalimido group), 7.59–7.65 (2H, m, AA′ part of AA′XX′ spin system, $C_{(2)}$H and $C_{(6)}$H in 4-MeC_6H_4), 7.53 (1H, dd, $^3J_{N(3)H,4-H}$=2.7, $^4J_{N(3)H,N(1)H}$=1.8 Hz, $N_{(3)}$H), 7.24–7.30 (2H, m, XX′ part of AA′XX′ spin system, $C_{(3)}$H and $C_{(5)}$H in 4-MeC_6H_4), 5.27 (1H, ddd, $^3J_{4-H,5-H(A)}$=9.1, $^3J_{4-H,N(3)H}$=2.7, $^3J_{4-H,5-H(B)}$=2.5 Hz, 4-H), 3.23 (1H, dd, $^2J_{5-H(A),5-}$

$_{H(B)}$=15.0, $^{3}J_{5\text{-}H(A),4\text{-}H}$=9.1 Hz, 5-H(A)), 2.92 (1H, dd, $^{2}J_{5\text{-}H(B),5\text{-}H(A)}$=15.0, $^{3}J_{5\text{-}H(B),4\text{-}H}$=2.5 Hz, 5-H(B)), 2.29 (3H, s, CH_3 in Ts), 2.28 (3H, s, 7-CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 166.9 (C=O in phthalimido group), 153.8 ($C_{(2)}$), 148.7 ($C_{(7)}$), 143.6 ($C_{(4)}$ in 4-MeC_6H_4), 139.1 ($C_{(1)}$ in 4-MeC_6H_4), 134.6 ($C_{(4)}$ and $C_{(5)}$ in phthalimido group), 131.4 ($C_{(1)}$ and $C_{(2)}$ in phthalimido group), 129.9 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 126.4 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 123.1 ($C_{(3)}$ and $C_{(6)}$ in phthalimido group), 114.2 ($C_{(6)}$), 61.1 ($C_{(4)}$), 30.9 ($C_{(5)}$), 21.1 (CH_3 in Ts), 19.2 (7-CH_3). IR (Nujol): ν=3380s, 3362s, 3241s, 3123s, 3108s (ν NH), 3063w (ν CH_{arom}), 1774m, 1717s (amide-I in phthalimido group), 1680s (amide-I in diazepinone moiety), 1633s (ν C=C), 1598w (ν CC_{arom}), 1316s (ν_{as} SO_2), 1144s (ν_s SO_2), 812m (δ CH_{arom} in Ts), 723s (δ CH in phthalimido group). Anal. Calcd for $C_{21}H_{19}N_3O_5S$: C, 59.28; H, 4.50; N, 9.88. Found: C, 59.45; H, 4.81; N, 10.17.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.06.089. These data include MOL files and InChIKeys of the most important compounds described in this article.

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13. The PM6 calculations were carried out using the Mopac 2009 (James J. P. Stewart, Stewart Computational Chemistry, Version 9.211W, http://openmopac.net/index.html).