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4-Hydroxy-4-methyl-5-tosylhexahydropyrimidin-2-imines: synthesis and different dehydration pathways

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ABSTRACT

Synthesis of 4-hydroxy-4-methyl-5-tosylhexahydropyrimidin-2-imines by reaction of *N*-cyano-*N*′-(1-tosylalk-1-yl)guanidines with enolates of tosylacetone was developed. Base-catalyzed dehydration of the obtained pyrimidines gave the expected 6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-imines. However, their acid-catalyzed dehydration led to mixtures of the latter compounds and the products of tosyl group migration, 4-tosylmethyl derivatives. This reaction was strongly influenced by the nature of the solvent. Plausible explanations of the obtained data were given.

1. Introduction

Recently, we have developed a new general approach to 5-functionalized 4-hydroxyhexahydropyrimidine-2-thiones/ones **1a**,**b** and 1,2,3,4-tetrahydropyrimidine-2-thiones/ones **2a**,**b** (Fig. 1) by the reaction of readily available *N*-(1-tosylalk-1-yl)thioureas and *N*-(1-tosylalk-1-yl)ureas with enolates of α-substituted carbonyl compounds.[1]

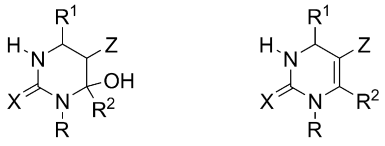


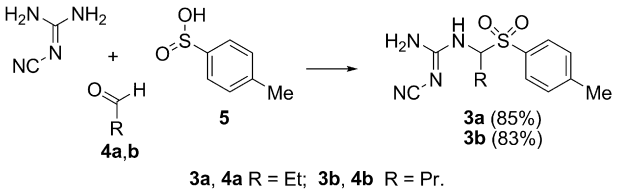
Fig. 1. Structures of 5-functionalized 4-hydroxyhexahydropyrimidine-2-thiones(ones, imines) **1a**–**c** and 1,2,3,4-tetrahydropyrimidine-2-thiones(ones, imines) **2a**–**c**.

We hypothesized that the same synthetic approach might be applicable to the preparation of 5-functionalized 4-hydroxyhexahydropyrimidin-2-imines **1c** and 1,2,3,4-tetrahydropyrimidin-2-imines **2c** (Fig. 1). These compounds are currently of great interest because some of them are the constituents of the natural guanidine alkaloids (e.g., tetrodotoxin, ptilocaulin, saxitoxin, batzelladine B, crambescin B, etc.), which possess a variety of biological activities.[2] In this communication, we describe a novel synthesis of tosyl-substituted 2-cyanoiminohexahydropyrimidines and 2-cyanoimino-1,2,3,4-tetrahydropyrimidines using α-guanidinoalkylation as a key step.

2. Results and discussion

2.1. Reaction of α-tosyl-substituted *N*-alkyl-*N*′-cyanoguanidines with enolates of tosylacetone

Starting materials, α-tosyl-substituted *N*-alkyl-*N*′-cyanoguanidines **3a**,**b**, were obtained by the three-component condensation of equivalent amounts of cyanoguanidine, aliphatic aldehydes **4a**,**b** and *p*-toluenesulfinic acid (**5**) in water at rt (Scheme 1). Although the reaction time was substantially longer (3–4 days) than in the case of thioureas and ureas,[1] **3a**,**b** were obtained in 85 and 83%



Scheme 1. Synthesis of *N*-cyano -*N*′-(1-tosylalk-1-yl)guanidines **3a**,**b**.

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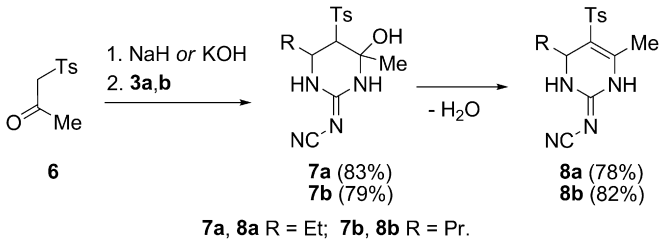
yields, respectively. The purity of the crude **3a**,**b** was excellent (>94% according to ^{1}H NMR data), therefore, they were used in further transformations without additional purification.

The obtained sulfones **3a**,**b** reacted at rt with sodium or potassium enolates of tosylacetone (**6**) generated by treatment of **6** with NaH or KOH at rt to produce expected 4-hydroxyhexahydropyrimidin-2-imines **7a**,**b** (Scheme 2).



Scheme 2. Reaction of *N*-cyano-*N*′-(1-tosylalk-1-yl)guanidines **3a**,**b** with enolates of tosylacetone (**6**).

When α-tosyl-substituted *N*-alkyl(thio)ureas were used as starting compounds in the reaction with enolates of α-functionalized ketones under the similar conditions, hydroxypyrimidines **1a**,**b** were the only products.[1] In contrast, some amount of the respective tetrahydropyrimidines **8a**,**b** (Table 1) always formed in the reaction of enolates of **6** with tosylguanidines **3a**,**b**. The yield of **8a**,**b** increased when MeCN was used instead of THF (entry 2 vs entry 3; entry 7 vs entry 8), with prolonged reaction time (entry 1 vs entry 2; entry 4 vs entry 5; entry 8 vs entry 9 vs entry 10), and at higher reaction temperature (entry 4 vs entry 6). Under more forcing conditions, spectroscopically pure **8a**,**b** were obtained in good yields (entries 5, 6 and 11). On the other hand, under the optimal conditions (NaH, THF, rt, 2.6–3.5 h) the hydroxypyrimidines **7a**,**b** formed contained only the small amount (6–7 mol %) of **8a**,**b** (entries 1 and 7).

couplings observed. For compound **7a** the position of the hydroxyl group was determined using ^{1}H,^{1}H-NOESY experiments (Fig. 2). NOEs were observed between the OH and 5-H protons and between one of the hydrogens of the exocyclic methylene group and OH. These and other NOE relationships in the major diastereomer of **7a** confirmed the axial orientation of OH, Ts and Et groups. Thus, this isomer has the (4*R**,5*S**,6*S**)-configuration. Comparison of ^{1}H and ^{13}C NMR spectra of **7a** and **7b** allowed us to conclude that the major diastereomer of **7b** has the same (4*R**,5*S**,6*S**)-configuration.

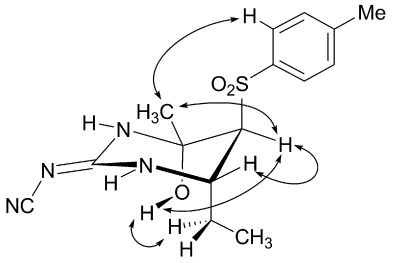


Fig. 2. Diagnostic NOE relationships in (4*R**,5*S**,6*S**)-**7a**.

Three-dimensional structures of minor isomers of **7a**,**b** could not be unambiguously determined by ^{1}H NMR spectroscopy because of their small quantities in the obtained products (Table 1). However, based on the presence of the long range coupling constant $^4J_{OH,5\text{-}H}$=1.0 Hz in ^{1}H NMR spectrum of the minor isomer of **7b** in DMSO-d_6, we concluded that the hydroxyl and tosyl groups in this isomer have axial and equatorial orientation, respectively. Presumably, the minor diastereomer of **7b** differs from the major one only in the orientation of the tosyl group and therefore has (4*R**,5*R**,6*S**)-configuration. The same configuration has one of the minor diastereomers of **7a** (δ OH=6.38 ppm, doublet, $^4J_{OH,5\text{-}H}$=1.2 Hz).

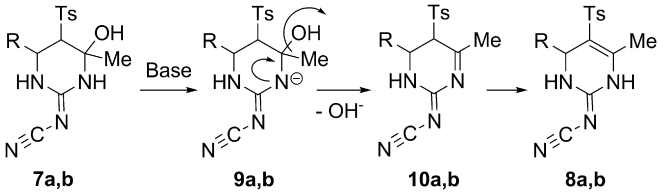
Thus, high tendency of compounds **7a**,**b** to dehydration is caused by 1,3-diaxial repulsion between the alkyl group at C6 and

Table 1
Reaction of guanidines **3a**,**b** with tosylacetone (**6**) in the presence of bases

Entry	Guanidine **3**	Base	Solvent	Reaction conditions	Product(s)	**7**/**8** molar ratio[a]	Yield **7**+**8**, %[b]	Diastereomer ratio of **7**[c]
1	**3a**	NaH	THF	rt, 2.6 h	**7a**, **8a**	93:7	83	96:3:1
2	**3a**	NaH	THF	rt, 7.4 h	**7a**, **8a**	83:17	90	95:2:3
3	**3a**	NaH	MeCN	rt, 7.5 h	**7a**, **8a**	78:22	81	89:11
4	**3a**	KOH	EtOH	rt, 24.3 h	**7a**, **8a**	26:74	90	74:26
5	**3a**	KOH	EtOH	rt, 47.5 h	**7a**, **8a**	4:96	78	66:34
6	**3a**	KOH	EtOH	rt, 7.5 h, then reflux, 1.5 h	**8a**	0:100	64	—
7	**3b**	NaH	THF	rt, 3.5 h	**7b**, **8b**	94:6	79	79:21
8	**3b**	NaH	MeCN	rt, 4 h	**7b**, **8b**	75:25	82	74:26
9	**3b**	NaH	MeCN	rt, 6.1 h	**7b**, **8b**	69:31	81	72:28
10	**3b**	NaH	MeCN	rt, 10 h	**7b**, **8b**	46:54	80	82:18
11	**3b**	KOH	EtOH	rt, 47.3 h	**7b**, **8b**	2:98	82	67:33

[a] According to ^{1}H NMR data of the crude products.
[b] Calculated using **7**/**8** molar ratios.
[c] Determined by integration of the signals of OH protons (6.08–6.38 ppm range) in ^{1}H NMR spectra of the crude products in DMSO-d_6.

We supposed that a pronounced tendency of hydroxypyrimidin-2-imines **7a**,**b** to dehydration could be explained by the three-dimensional structure of these compounds. According to ^{1}H NMR data, they formed as a mixture of two or three diastereomers with a great predominance of one of them (Table 1).[3] The major isomer of **7a**,**b** has axial orientation of the alkyl group at C6, which follows from the value of the coupling constant $^3J_{N(1)H,6\text{-}H}$=4.4–4.5 Hz.[4] The value of the characteristic coupling constant $^3J_{5\text{-}H,6\text{-}H}$ was close to zero thus confirming that the respective dihedral angle was almost 90°. Calculations of geometry of the hydroxypyrimidines **7a**,**b** with various orientations of substituents at C5 and C4 using semi-empirical methods AM1 and PM6[5] showed that only the axial orientation of the tosyl group could be in agreement with the the hydroxyl group at C4. We suppose that, because of the basicity of the reaction media, this dehydration proceeds via E1cB mechanism (Scheme 3).

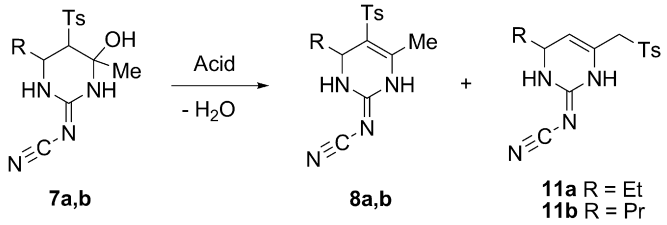


Scheme 3. Mechanism of base-catalyzed dehydration of **7a**,**b**.

According to this mechanism, deprotonation of $N_{(3)}H$ with a base followed by OH-anion elimination from the obtained anions **9a**,**b**, which is favoured by stereoelectronic factors[6] leads to formation of tetrahydropyrimidines **10a**,**b**. The latter undergo an imine–enamine tautomeric shift to give **8a**,**b**.

2.2. Acid-catalyzed dehydration of 4-hydroxy-5-tosylhexahydropyrimidin-2-imines. Tosyl group migration

We found that acid-catalyzed dehydration of hydroxypyrimidines **7a**,**b** using 25 mol % TsOH in refluxing EtOH gave predominantly products of the tosyl group migration, pyrimidines **11a**,**b**, along with small amounts (6–11%) of the expected **8a**,**b** (Scheme 4) (Table 2, entries 2 and 6). In contrast, the migration of tosyl group under the similar conditions was not observed in case of dehydration of 4-hydroxy-4-methyl-5-tosylhexahydropyrimidine-2-thiones/ones.[1c,7]



7a,b 8a,b

Scheme 4. Acid-catalyzed dehydration of **7a**,**b**.

Table 2
The influence of the solvent and catalyst on the ratio of **8**/**11** in the acid-catalyzed dehydration of **7**

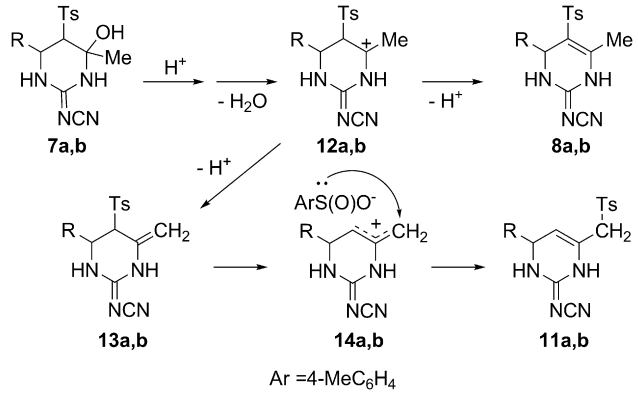
Entry	Pyrimidine **7**	Solvent	Catalyst	Products	Yield **8**+**11**, %	**8**/**11** molar ratio[a]
1	**7a**	MeCN	TsOH	**8a**, **11a**	95	50:50
2	**7a**	EtOH	TsOH	**8a**, **11a**	79	11:89
3	**7a**	EtOH/H_2O	TsOH	**8a**, **11a**	77	26:74
4	**7a**	EtOH	4-MeC_6H_4SOOH	**8a**, **11a**	77	35:65
5	**7b**	MeCN	TsOH	**8b**, **11b**	100	63:37
6	**7b**	EtOH	TsOH	**8b**, **11b**	93	6:94
7	**7b**	EtOH/H_2O	TsOH	**8b**, **11b**	81	16:84

[a] According to ^{1}H NMR data of the crude products.

The unexpected formation of **11a**,**b** led us to study the acid-catalyzed dehydration of hydroxypyrimidines **7a**,**b** in more detail (Table 2). The ratios of **11** to **8** were strongly affected by the solvent used. Thus, the percentage of **11a** increased from 50 to 89% when protic EtOH was applied instead of aprotic MeCN (entry 1 vs entry 2). The further increase in the solvation strength of the reaction media decreased the amount of **11a** to 74% (entry 2 vs entry 3). An analogous solvent effect was observed for **7b** (entries 5, 6 and 7). Increase in acidity of the catalyst favoured formation of compound **11a** (entry 2 vs entry 4).

Transformation of **7a**,**b** into **8a**,**b** and **11a**,**b** is kinetically controlled. Indeed, after treatment of **8a** or **11b** with 30 mol % of TsOH (EtOH, reflux, 5 h and MeCN, reflux, 40 min, respectively) only the starting compounds were recovered.

Scheme 5 shows a plausible pathway for the transformation of **7a**,**b** into **8a**,**b** and **11a**,**b** under acidic conditions. The first step of the reaction involves formation of intermediate acyliminium cations **12a**,**b**. The following proton loss from **12a**,**b** gives either tetrahydropyrimidines **8a**,**b** or 4-methylenpyrimidines **13a**,**b**. The allylic rearrangement of **13a**,**b** with tosyl group migration proceeds via carbocations **14a**,**b** and results in the formation of **11a**,**b**. According to our experimental data (Table 2), the increase of the solvation ability of the reaction media favours formation of cations **14a**,**b** and facilitates the rearrangement.



Scheme 5. A plausible pathway for transformation of **7a**,**b** into **8a**,**b** and **11a**,**b** under acidic conditions.

Transformation of **7a**,**b** into **11a**,**b** via 4-methylenpyrimidines **13a**,**b** is confirmed by the direct observation of **13a**,**b** in some cases during crystallization of **7a**,**b** from MeCN. Thus, a mixture of **13a**,[8] **11a** and **7a** in a ratio of 86:11:3 was obtained from **7a**, and a mixture of **13b**,[9] **11b**, **8b** and **7b** in a ratio of 46:23:14:17 was prepared from **7b**.

The hypothetic reaction pathway described above is consistent with a higher stability of allylsulfones in comparison with vinylsulfones[10] and migration ability of arylsulfonyl groups in allylsulfones.[11]

3. Conclusion

In summary, a convenient method for the synthesis of previously unknown 2-cyanoimino-4-hydroxy-4-methyl-5-tosylhexahydropyrimidines by reaction of *N*-cyano-*N*′-(1-tosylalk-1-yl) guanidines with tosylacetone in the presence of bases was developed. The obtained compounds readily dehydrated under basic conditions to give the expected 2-cyanoimino-5-tosyl-1,2,3,4-tetrahydropyrimidines. In contrast, the dehydration under acidic conditions afforded also the products of the tosyl group migration, 2-cyanoimino-4-tosylmethyl-1,2,3,4-tetrahydropyrimidines. Protic solvents strongly favoured this migration. The mechanisms of these reactions were discussed.

4. Experimental section

4.1. General

Acetonitrile was dried by distillation from P_2O_5 and then from CaH_2. *p*-Toluenesulfinic acid (**5**) was synthesized by treatment of a saturated aqueous solution of sodium *p*-toluenesulfinate[12] 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 dry hexane, dried in vacuum desiccator prior to use. All other reagents and solvents were purchased from commercial sources and used without further treatment.

IR spectra (in Nujol or KBr pellet) were recorded using a Bruker Equinox 55/S and Perkin–Elmer Spectrum BX spectrophotometers. Peak intensities in the IR spectra are defined as strong (s), medium (m) or weak (w). NMR spectra were recorded on a Bruker DPX-300 spectrometer at 300.13 (^{1}H) and 75.48 (^{13}C) MHz and a Bruker Avance 600 spectrometer at 600.13 MHz (^{1}H) as solutions in DMSO-d_6. ^{1}H NMR chemical shifts are referenced to the residual proton signal for DMSO-d_6 (2.50 ppm). ^{13}C NMR chemical shifts are reported to the carbon signal for DMSO-d_6 (39.50 ppm). Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), some combination 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. Plates were visualised with iodine vapour or UV light. All yields refer to isolated, spectroscopically and TLC pure compounds.

*4.1.1. N-Cyano-N′-(1-tosylpropyl)guanidine (**3a**).* To a mixture of propanal (3.041 g, 52.36 mmol) and H_2O (60 mL) was added *p*-toluenesulfinic acid (8.182 g, 52.38 mmol) under stirring followed by the addition of H_2O (15 mL). After 10 min to the obtained white suspension were added finely powdered cyanoguanidine (4.402 g, 52.35 mmol) and H_2O (15 mL). The reaction mixture was left at rt for 70 h, occasionally stirring it. Upon cooling to 0 °C, the white precipitate was filtered, washed with ice-cold water, hexane, and dried to give 12.536 g (85%) of **3a**, which was used without further purification. An analytically pure sample was obtained by recrystallization from MeCN. Mp 154.5–155 °C (MeCN). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.67–7.72 (2H, m, AA′ part of AA′XX′ spin system, $C_{(2)}$H and $C_{(6)}$H in 4-MeC_6H_4), 7.61 (1H, d, $^3J_{NH,CH}$=9.7 Hz, NH), 7.42–7.47 (2H, m, XX′ part of AA′XX′ spin system, $C_{(3)}$H and $C_{(5)}$H in 4-MeC_6H_4), 6.79 (2H, br s, NH_2), 4.94 (1H, ddd, $^3J_{CH,CH(B)}$=10.7, $^3J_{CH,NH}$=9.7, $^3J_{CH,CH(A)}$=3.1 Hz, CH–SO_2), 2.41 (3H, s, CH_3 in Ts), 1.91–2.10 (1H, unresolved m, CH(A) in CH_2), 1.60 (1H, ddq, $^2J_{CH(B),CH(A)}$=13.8, $^3J_{CH(B),CH}$=10.7, $^3J_{CH(B),CH3}$=7.3 Hz, CH(B) in CH_2), 0.91 (3H, t, $^3J_{CH3,CH(A)}$=$^3J_{CH3,CH(B)}$=7.3 Hz, CH_3 in Et). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 160.9 (N–C=N), 144.8 ($C_{(4)}$ in 4-MeC_6H_4), 133.7 ($C_{(1)}$ in 4-MeC_6H_4), 129.7 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 128.9 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 116.6 (C≡N), 71.7 (CH–N), 21.2 (CH_3 in Ts), 20.1 (CH_2 in Et), 9.7 (CH_3 in Et). IR (Nujol) ν, cm^{-1}: 3423 (s), 3335 (s), 3274 (m), 3218 (w), 3173 (m), 3125 (w) (ν NH), 3070 (w), 3048 (w) (ν CH_{arom}), 2180 (s), 2166 (s) (ν C≡N), 1635 (s) [NH–C(=N)–NH], 1599 (m) (ν CC in Ts), 1538 (s) [NH–C(=N)–NH], 1495 (w) (ν CC in Ts), 1313 (s) (ν_{as} SO_2), 1143 (s) (ν_s SO_2), 815 (s) (δ CH_{arom}). Anal. Calcd for $C_{12}H_{16}N_4O_2S$: C, 51.41; H, 5.75; N 19.99. Found: C, 51.49; H, 6.04; N, 19.70.

*4.1.2. N-Cyano-N′-(1-tosylbutyl)guanidine (**3b**).* Compound **3b** (6.842 g, 83%) was synthesized as a white solid in the same way as **3a** by reaction of butanal (2.019 g, 28.01 mmol) with *p*-toluenesulfinic acid (4.372 g, 27.99 mmol) and cyanoguanidine (2.356 g, 52.35 mmol) in water (50 mL) at rt for 90 h. Mp 161.5–162 °C (decomp., MeCN). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.67–7.72 (2H, m, AA′ part of AA′XX′ spin system, $C_{(2)}$H and $C_{(6)}$H in 4-MeC_6H_4), 7.62 (1H, br d, $^3J_{NH,CH}$=9.8 Hz, NH), 7.42–7.47 (2H, m, XX′ part of AA′XX′ spin system, $C_{(3)}$H and $C_{(5)}$H in 4-MeC_6H_4), 6.77 (2H, br s, NH_2), 4.99 (1H, ddd, $^3J_{CH,CH(B)}$=11.1, $^3J_{CH,NH}$=9.8, $^3J_{CH,CH(A)}$=3.1 Hz, CH–SO_2), 2.41 (3H, s, CH_3 in Ts), 1.82–2.00 (1H, unresolved m, CH(A) in CH_2), 1.60 (1H, dddd, $^2J_{CH(B),CH(A)}$=13.6, $^3J_{CH(B),CH}$=11,1, $^3J_{CH(B),CH(A′)}$=8.7, $^3J_{CH(B),CH(B′)}$=4.8 Hz, CH(B) in CH_2), 1.18–1.48 (2H, m, CH(A′) and CH(B′) in CH_2), 0.86 (3H, t, $^3J_{CH3,CH2}$=7.3 Hz, CH_3 in Pr). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 160.8 (N–C=N), 144.8 ($C_{(4)}$ in 4-MeC_6H_4), 133.6 ($C_{(1)}$ in 4-MeC_6H_4), 129.7 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 128.9 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 116.6 (C≡N), 70.1 (CH–N), 28.1 (CH_2 in Pr), 21.1 (CH_3 in Ts), 18.0 (CH_2 in Pr), 13.2 (CH_3 in Pr). IR (KBr) ν, cm^{-1}: 3429 (s), 3340 (s), 3265 (m), 3172 (m), 3123 (w) (ν NH), 3068 (w), 3003 (w) (ν CH_{arom}), 2181 (s), 2164 (s) (ν C≡N), 1637 (s) [NH–C(=N)–NH], 1597 (m) (ν CC in Ts), 1541 (s) [NH–C(=N)–NH], 1312 (s) (ν_{as} SO_2), 1142 (s) (ν_s SO_2), 813 (m) (δ CH_{arom}). Anal. Calcd for $C_{13}H_{18}N_4O_2S$: C, 53.04; H, 6.16; N, 19.03. Found: C, 53.01; H, 6.35; N, 18.92.

*4.1.3. 2-(Cyanimino)-6-ethyl-4-hydroxy-4-methyl-5-tosylhexahydropyrimidine (**7a**).* To a mixture of tosylacetone (**6**) (0.805 g, 3.79 mmol) and NaH (0.092 g, 3.83 mmol) was added anhydrous THF (5 mL), and the obtained mixture was stirred for 7 min upon cooling on ice-bath. Then to the resulting solution were added guanidine **3a** (1.065 g, 3.80 mmol) and anhydrous THF (2.6 mL). The formed suspension was stirred at rt for 2.6 h, and the solvent was removed in vacuum. The white solid residue was triturated with hexane (5 mL), a saturated aqueous solution of $NaHCO_3$ (2 mL) was added and the obtained dense suspension was left in a water bath (bath temperature 32 °C) for 3.5 h. Upon cooling to 0 °C, the white precipitate was filtered, washed with ice-cold water, hexane, dried, washed with cold (0 °C) ether (2×5 mL), and dried to give 1.058 g of product as a 93:7 mixture of hydroxypyrimidine **7a** (three diastereomers, 96:3:1) and tetrahydropyrimidine **8a** (Table 1, entry 1).[13] The yield calculated for pure **7a** is 83%. An analytically pure sample of **7a** (two diastereomers, 98:2) was obtained by rapid crystallization from MeCN.[14] Mp 150–151 °C (decomp., MeCN). ^{1}H NMR of the major isomer (600.13 MHz, DMSO-d_6) δ: 8.08 (1H, d, $^4J_{N(3)H,N(1)H}$=2.0 Hz, $N_{(3)}$H), 7.76–7.79 (2H, m, AA′ part of AA′XX′ spin system, $C_{(2)}$H and $C_{(6)}$H in 4-MeC_6H_4), 7.72 (1H, dd, $^3J_{N(1)H,6\text{-}H}$=4.4, $^4J_{N(1)H,N(3)H}$=2.0 Hz, $N_{(1)}$H), 7.44–7.47 (2H, m, XX′ part of AA′XX′ spin system, $C_{(3)}$H and $C_{(5)}$H in 4-MeC_6H_4), 6.08 (1H, s, OH), 3.67 (1H, d, $^3J_{5\text{-}H,6\text{-}H}$=0.7 Hz, 5-H), 3.62 (1H, dddd, $^3J_{6\text{-}H,CH(A)}$=8.8, $^3J_{6\text{-}H,CH(B)}$=6.4, $^3J_{6\text{-}H,N(1)H}$=4.4, $^3J_{6\text{-}H,5\text{-}H}$=0.7 Hz, 6-H), 2.42 (3H, s, CH_3 in Ts), 1.86 (1H, ddq, $^2J_{CH(A),CH(B)}$=13.3, $^3J_{CH(A),6\text{-}H}$=8.8, $^3J_{CH(A),CH3}$=7.4 Hz, CH(A) in 6-CH_2), 1.70 (1H, ddq, $^2J_{CH(B),CH(A)}$=13.3, $^3J_{CH(B),6\text{-}H}$=6.4, $^3J_{CH(B),CH3}$=7.4 Hz, CH(B) in 6-CH_2), 1.68 (3H, s, 4-CH_3), 0.61 (3H, t, $^3J_{CH3,CH(A)}$=$^3J_{CH3,CH(B)}$=7.4 Hz, CH_3 in Et). ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 7.98 (1H, br s, $N_{(3)}$H), 6.38 (1H, d, $^4J_{OH,5\text{-}H}$=1.2 Hz, OH), 1.74 (3H, s, 4-CH_3), 0.75 (3H, t, $^3J_{CH3,CH2}$=7.3 Hz, CH_3 in Et). Signals of other protons overlap with proton signals of the major isomer. ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 155.8 ($C_{(2)}$), 144.8 ($C_{(4)}$ in 4-MeC_6H_4), 135.4 ($C_{(1)}$ in 4-MeC_6H_4), 129.8 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 128.5 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 117.7 (C≡N), 78.1 ($C_{(4)}$), 64.1 ($C_{(5)}$), 51.3 ($C_{(6)}$), 28.5 (CH_2 in Et), 28.1 (4-CH_3), 21.1 (CH_3 in Ts), 10.0 (CH_3 in Et). IR (Nujol) ν, cm^{-1}: 3435 (m), 3264 (sh), 3191 (s), ~3130 (sh) (ν NH, ν OH), 2179 (s) (ν C≡N), 1653 (s) [NH–C(=N)–NH], 1596 (m) (ν CC in Ts), 1564 (s) [NH–C(=N)–NH], 1303 (s) (ν_{as} SO_2), 1142 (s) (ν_s SO_2), 814 (s) (δ CH_{arom}). Anal. Calcd for $C_{15}H_{20}N_4O_3S$: C, 53.56; H, 5.99; N, 16.65. Found: C, 53.53; H, 6.00; N, 16.48.

*4.1.4. 2-(Cyanimino)-4-hydroxy-4-methyl-6-propyl-5-tosylhexahydropyrimidine (**7b**).* Compound **7b** was synthesized as a white solid in the same way as **7a** from tosylacetone (**6**) (1.069 g, 5.04 mmol), NaH (0.122 g, 5.08 mmol) and guanidine **3b** (1.482 g, 5.03 mmol) in anhydrous THF (15 mL) at rt for 3.5 h. The obtained product (1.384 g) was a 94:6 mixture of hydroxypyrimidine **7b** (two diastereomers, 79:21) and tetrahydropyrimidine **8b** (Table 1, entry 7).[15] The yield calculated for pure **7b** is 79%. An analytically pure sample of **7b** (two diastereomers, 98:2) was obtained by rapid crystallization from MeCN.[14] Mp 148.5–150 °C (decomp., MeCN). ^{1}H NMR of the major isomer (600.13 MHz, DMSO-d_6) δ: 8.06 (1H, d, $^4J_{N(3)H,N(1)H}$=1.6 Hz, $N_{(3)}$H), 7.76–7.79 (2H, m, AA′ part of AA′XX′ spin system, $C_{(2)}$H and $C_{(6)}$H in 4-MeC_6H_4), 7.74 (1H, dd, $^3J_{N(1)H,6\text{-}H}$=4.5, $^4J_{N(1)H,N(3)H}$=1.6 Hz, $N_{(1)}$H), 7.44–7.47 (2H, m, XX′ part of AA′XX′ spin system, $C_{(3)}$H and $C_{(5)}$H in 4-MeC_6H_4), 6.08 (1H, s, OH), 3.74 (1H, ddd, $^3J_{6\text{-}H,CH(B)}$=8.4, $^3J_{6\text{-}H,CH(A)}$=6.3, $^3J_{6\text{-}H,N(1)H}$=4.5 Hz, 6-H), 3.66 (1H, s, 5-H), 2.42 (3H, s, CH_3 in Ts), 1.80–1.87 and 1.63–1.69 (1H each, two m, $CH_2CH_2CH_3$), 1.67 (3H, s, 4-CH_3), 1.13–1.22 and 0.92–1.01 (1H each, two m, $CH_2CH_2CH_3$), 0.68 (3H, t, $^3J_{CH3,CH2}$=7.4 Hz, CH_3 in Pr). ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 7.94 (1H, d, $^4J_{N(3)H,N(1)H}$=1.9 Hz, $N_{(3)}$H), 6.36 (1H, d, $^4J_{OH,5\text{-}H}$=1.0 Hz, OH), 2.41 (3H, s, CH_3 in Ts), 1.73 (3H, s, 4-CH_3), 0.79 (3H, t, $^3J_{CH3,CH2}$=7.2 Hz, CH_3 in Pr). Signals of other protons overlap with proton signals of the major isomer. ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 155.8 ($C_{(2)}$), 144.7 ($C_{(4)}$ in 4-MeC_6H_4), 135.4 ($C_{(1)}$ in 4-MeC_6H_4), 129.8 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 128.4 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 117.7 (C≡N), 78.1 ($C_{(4)}$), 64.7 ($C_{(5)}$), 49.2 ($C_{(6)}$), 37.8 (CH_2 in Pr), 28.1 (4-CH_3), 21.1 (CH_3

in Ts), 18.2 (CH_2 in Pr), 13.2 (CH_3 in Pr). IR (KBr) ν, cm^{-1}: 3434 (s), 3255 (s) (ν NH, ν OH), 2174 (s) (ν C≡N), 1631 (s) [NH–C(=N)–NH], 1597 (w) (ν CC in Ts), 1562 (s) [NH–C(=N)–NH], 1492 (w) (ν CC in Ts), 1303 (s) (ν_{as} SO_2), 1141 (s) (ν_s SO_2), 815 (s) (δ CH_{arom}). Anal. Calcd for $C_{16}H_{22}N_4O_3S$: C, 54.84; H, 6.33; N, 15.99. Found: C, 54.62; H, 6.60; N, 15.84.

*4.1.5. 2-Cyanimino-4-ethyl-6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidine (**8a**). Method A.* To a stirred solution of KOH (0.117 g, 2.09 mmol) in EtOH (3 mL) at rt was added tosylacetone (**6**) (0.423 g, 1.99 mmol) at once. After 5 min to the obtained solution were added guanidine **3a** (0.588 g, 2.00 mmol) and EtOH (2 mL). The resulting solution was stirred at rt for 47.5 h, the solvent was removed under vacuum and the oily residue was triturated with light petrol (3 mL) and saturated aqueous solution of $NaHCO_3$ (1.5 mL) until crystallization. The obtained suspension was left overnight at rt, the white precipitate was filtered, washed with water, light petrol, dried, washed with ether (2×3 mL), and dried to give 0.499 g of product as a 96:4 mixture of **8a** and hydroxypyrimidine **7a** (two diastereomers, 66:34) (Table 1, entry 5). The yield calculated for pure **8a** is 78%. An analytically pure sample of **8a** was obtained by crystallization from MeCN. Mp 226–226.5 °C (decomp., MeCN). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.23 (1H, s, $N_{(1)}H$), 8.83 (1H, d, $^3J_{N(3)H,4\text{-}H}$=3.8 Hz, $N_{(3)}H$), 7.70–7.76 (2H, m, AA′ part of AA′XX′ spin system, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.40–7.46 (2H, m, XX′ part of AA′XX′ spin system, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 4.10 (1H, dt, $^3J_{4\text{-}H,CH2}$=5.6, $^3J_{4\text{-}H,N(3)H}$=3.8 Hz, 4-H), 2.40 (3H, s, CH_3 in Ts), 2.20 (3H, s, 6-CH_3), 1.54 (2H, dq, $^3J_{CH2,CH3}$=7.4, $^3J_{CH2,4\text{-}H}$=5.6 Hz, CH_2 in Et), 0.80 (3H, t, $^3J_{CH3,CH2}$=7.4 Hz, CH_3 in Et). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 155.7 ($C_{(2)}$), 145.6 ($C_{(6)}$), 143.9 ($C_{(4)}$ in 4-MeC_6H_4), 139.5 ($C_{(1)}$ in 4-MeC_6H_4), 130.0 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 126.4 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 116.2 (C≡N), 109.7 ($C_{(5)}$), 51.3 ($C_{(4)}$), 29.5 (CH_2 in Et), 21.0 (CH_3 in Ts), 16.2 (CH_3), 8.0 (CH_3 in Et). IR (Nujol) ν, cm^{-1}: 3193 (s), 3057 (s) (ν NH), 2205 (s), 2179 (s) (ν C≡N), 1660 (sh), 1655 (s) [NH–C(=N)–NH], 1599 (w) (ν CC in Ts), 1523 (s) [NH–C(=N)–NH], 1492 (w) (ν CC in Ts), 1309 (s) (ν_{as} SO_2), 1155 (s) (ν_s SO_2), 810 (s) (δ CH_{arom}). Anal. Calcd for $C_{15}H_{18}N_4O_2S$: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.41; H, 5.81; N, 17.61.

Method B. To a stirred solution of KOH (0.214 g, 3.81 mmol) in EtOH (6 mL) at rt was added tosylacetone (**6**) (0.810 g, 3.82 mmol) at once. After 4 min to the obtained solution were added guanidine **3a** (1.075 g, 3.83 mmol) and EtOH (6.8 mL). The resulting solution was stirred at rt for 7 h, then at reflux for 1.5 h. The reaction mixture was neutralized with 18% aqueous solution of HCl to pH 5, the solvent was removed under vacuum and the oily residue was triturated with light petrol (2×3 mL) followed by decantation. To the obtained residue was added saturated aqueous solution of $NaHCO_3$ (4 mL) and the mixture was allowed to stand overnight at rt. Upon cooling to 0 °C, the precipitate was filtered, washed with ice-cold water, hexane, and dried to give 0.777 g (64%) of **8a** (Table 1, entry 6) as a white solid.

*4.1.6. 2-(Cyanimino)-6-methyl-4-propyl-5-tosyl-1,2,3,4-tetrahydropyrimidine (**8b**).* Compound **8b** was synthesized as a white solid in the same way as **8a** according to *Method A* from tosylacetone (**6**) (0.681 g, 3.21 mmol), KOH (0.188 g, 3.36 mmol) and guanidine **3b** (0.944 g, 3.21 mmol) in EtOH (8 mL) at rt for 47.3 h. The obtained product (0.874 g) was a 98:2 mixture of **8b** and hydroxypyrimidine **7b** (two diastereomers, 67:33) (Table 1, entry 11). The yield calculated for pure **8b** is 82%. An analytically pure sample of **8b** was obtained by crystallization from MeCN. Mp 225–226 °C (decomp., MeCN). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.24 (1H, s, $N_{(1)}H$), 8.86 (1H, d, $^3J_{N(3)H,4\text{-}H}$=3.9 Hz, $N_{(3)}H$), 7.69–7.75 (2H, m, AA′ part of AA′XX′ spin system, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.41–7.46 (2H, m, XX′ part of AA′XX′ spin system, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 4.12 (1H, ddd, $^3J_{4\text{-}H,CH(A)}$=7.5, $^3J_{4\text{-}H,N(3)H}$=3.9, $^3J_{4\text{-}H,CH(B)}$=3.8 Hz, 4-H), 2.39 (3H, s, CH_3 in Ts), 2.19 (3H, s, 6-CH_3), 1.12–1.56 (4H, m, CH_2CH_2 in Pr), 0.83 (3H, t, $^3J_{CH3,CH2}$=7.2 Hz, CH_3 in Pr). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 155.6 ($C_{(2)}$), 145.5 ($C_{(6)}$), 143.9 ($C_{(4)}$ in 4-MeC_6H_4), 139.5 ($C_{(1)}$ in 4-MeC_6H_4), 130.1 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 126.4 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 116.3 (C≡N), 110.2 ($C_{(5)}$), 49.9 ($C_{(4)}$), 38.4 (CH_2 in Pr), 21.0 (CH_3 in Ts), 16.6 (CH_2 in Pr), 16.2 (6-CH_3), 13.5 (CH_3 in Pr). IR (Nujol) ν, cm^{-1}: 3193 (s), 3049 (s) (ν NH), 2204 (sh), 2192 (s) (ν C≡N), 1658 (sh), 1648 (s) [NH–C(=N)–NH], 1602 (w) (ν CC in Ts), 1520 (s) [NH–C(=N)–NH], 1495 (w) (ν CC in Ts), 1311 (s) (ν_{as} SO_2), 1156 (s) (ν_s SO_2), 808 (s) (δ CH_{arom}). Anal. Calcd for $C_{16}H_{20}N_4O_2S$: C, 57.81; H, 6.06; N, 16.85. Found: C, 57.77; H, 6.21; N, 16.82.

*4.1.7. 2-Cyanimino-4-ethyl-6-(tosylmethyl)-1,2,3,4-tetrahydropyrimidine (**11a**).* To a 91:9 mixture of hydroxypyrimidine **7a** and tetrahydropyrimidine **8a** (0.427 g) containing 0.390 g (1.16 mmol) of **7a** were added $TsOH·H_2O$ (0.065 g, 0.34 mmol) and EtOH (5 mL). The obtained suspension was refluxed for 1 h 20 min under stirring. At the start solid substance dissolved and after 3 min new white precipitate formed. After the reaction was complete, the solvent was removed in vacuum. To the solid residue was added a saturated aqueous solution of $NaHCO_3$ (1 mL) and the resulting substance was triturated under cooling until complete crystallization. The obtained suspension was cooled to 0 °C, the white precipitate was filtered, washed with ice-cold water, light petrol, ether, and dried to give 0.327 g of product as a mixture of **11a** and **8a** in a ratio of 79:21. The calculated overall yield of **11a** and **8a**, and **11a**/**8a** ratio based on the quantity of starting **7a** were 79% and 89:11, respectively (Table 2, entry 2). Crystallization of the mixture from EtOH afforded pure **11a**. Mp 238–238.5 °C (decomp., EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.86 (1H, s, $N_{(1)}H$), 7.89 (1H, d, $^3J_{N(3)H,4\text{-}H}$=2.3 Hz, $N_{(3)}H$), 7.72–7.78 (2H, m, AA′ part of AA′XX′ spin system, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.43–7.49 (2H, m, XX′ part of AA′XX′ spin system, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 4.57 (1H, br d, $^3J_{5\text{-}H,4\text{-}H}$=3.7 Hz, 5-H), 4.21 (1H, d, A part of AB spin system, $^2J_{AB}$=14.1 Hz, CH(A)–SO_2), 4.16 (1H, d, B part of AB spin system, $^2J_{AB}$=14.1 Hz, CH(B)–SO_2), 3.86 (1H, ddt, $^3J_{4\text{-}H,CH2}$=5.6, $^3J_{4\text{-}H,5\text{-}H}$=3.7, $^3J_{4\text{-}H,N(3)H}$=2.3 Hz, 4-H), 2.41 (3H, s, CH_3 in Ts), 1.54 (2H, dq, $^3J_{CH2,CH3}$=7.4, $^3J_{4\text{-}H,CH2}$=5.6 Hz, CH_2 in Et), 0.67 (3H, t, $^3J_{CH3,CH2}$=7.4 Hz, CH_3 in Et). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 155.6 ($C_{(2)}$), 144.6 ($C_{(4)}$ in 4-MeC_6H_4), 135.1 ($C_{(1)}$ in 4-MeC_6H_4), 129.7 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 128.1 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 124.8 ($C_{(6)}$), 116.8 (C≡N), 105.8 ($C_{(5)}$), 56.7 (CH_2–S), 51.4 ($C_{(4)}$), 29.8 (CH_2 in Et), 21.1 (CH_3 in Ts), 7.7 (CH_3 in Et). IR (Nujol) ν, cm^{-1}: 3202 (s), 3080 (m) (ν NH), 2185 (s) (ν C≡N), 1697 (m) (ν C=C), 1643 (s), 1632 (s), 1622 (sh) [NH–C(=N)–NH], 1537 (s) [NH–C(=N)–NH], 1495 (w) (ν CC in Ts), 1323 (s) (ν_{as} SO_2), 1163 (s) (ν_s SO_2), 812 (s) (δ CH_{arom}). Anal. Calcd for $C_{15}H_{18}N_4O_2S$: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.41; H, 5.71; N, 17.93.

*4.1.8. 2-Cyanimino-4-propyl-6-(tosylmethyl)-1,2,3,4-tetrahydropyrimidine (**11b**).* Compound **11b** was synthesized as a white solid in the same way as **11a** by refluxing hydroxypyrimidine **7b** (0.257 g, 0.73 mmol) and $TsOH·H_2O$ (0.042 g, 0.22 mmol) in EtOH (3 mL) for 2 min. The obtained product (0.224 g, 93%) was a mixture of **11b** and **8b** in a ratio of 94:6 (Table 2, entry 6). An analytically pure sample of **11b** was obtained by crystallization from EtOH. Mp 236.5–237 °C (decomp., EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.83 (1H, unresolved dd, $^4J_{N(1)H,N(3)H}$=1.9, $^4J_{N(1)H,5\text{-}H}$=1.6 Hz, $N_{(1)}H$), 7.88 (1H, unresolved ddd, $^3J_{N(3)H,4\text{-}H}$=2.4, $^4J_{N(3)H,N(1)H}$=1.9, $^4J_{N(3)H,5\text{-}H}$=1.6 Hz, $N_{(3)}H$), 7.72–7.77 (2H, m, AA′ part of AA′XX′ spin system, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.43–7.49 (2H, m, XX′ part of AA′XX′ spin system, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 4.56 (1H, dt, $^3J_{5\text{-}H,4\text{-}H}$=4.1, $^4J_{5\text{-}H,N(1)H}$=$^4J_{5\text{-}H,N(3)H}$=1.6 Hz, 5-H), 4.22 (1H, d, A part of AB spin system, $^2J_{AB}$=14.2 Hz, CH(A)–SO_2), 4.16 (1H, d, B part of AB spin system, $^2J_{AB}$=14.2 Hz, CH(B)–SO_2), 3.87 (1H, ddt, $^3J_{4\text{-}H,CH2}$=5.7, $^3J_{4\text{-}H,5\text{-}H}$=4.1, $^3J_{4\text{-}H,N(3)H}$=2.4 Hz, 4-H), 2.41 (3H, s, CH_3 in

Ts), 1.23–1.37 and 0.95–1.17 (2H each, two m, CH_2CH_2 in Pr), 0.81 (3H, t, $^3J_{CH3,CH2}$=7.2 Hz, CH_3 in Pr). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 155.6 ($C_{(2)}$), 144.6 ($C_{(4)}$ in 4-MeC_6H_4), 135.0 ($C_{(1)}$ in 4-MeC_6H_4), 129.7 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 128.2 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 124.6 ($C_{(6)}$), 116.8 (C≡N), 106.2 ($C_{(5)}$), 56.7 (CH_2–S), 50.3 ($C_{(4)}$), 39.3 (CH_2 in Pr), 21.1 (CH_3 in Ts), 16.5 (CH_2 in Pr), 13.7 (CH_3 in Pr). IR (KBr) ν, cm^{-1}: 3430 (s), 3207 (s), 3080 (s) (ν NH), 2183 (s) (ν C≡N), 1700 (m) (ν C=C), 1637 (s), 1627 (s) [NH–C(=N)–NH], 1598 (w) (H CC in Ts), 1539 (s) [NH–C(=N)–NH], 1497 (w) (H CC in Ts), 1320 (s) (H_{as} SO_2), 1162 (s) (ν_s SO_2), 811 (s) (δ CH_{arom}). Anal. Calcd for $C_{16}H_{20}N_4O_2S$: C, 57.81; H, 6.06; N, 16.85. Found: C, 58.05; H, 6.26; N, 16.75.

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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.2011.06.088. These data include MOL files and InChIKeys of the most important compounds described in this article.

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3. Crystallization of the diastereomeric mixtures of **7a**,**b** from MeCN gave the practically pure major isomers of these compounds (98 mol % according to ^1H NMR data).
4. Previously[16] we proposed a convenient criterion for the determination of the substituent orientation at C4 and C6 in hexahydropyrimidine-2-thiones/ones, which was based on the values of vicinal coupling constants $J_{N(1)H,6\text{-}H}$ and $J_{N(3)H,4\text{-}H}$.
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8. Spectral characteristics of **13a**: ^1H NMR (300.13 MHz, DMSO-d_6) δ: 9.90 (1H, d, $^4J_{N(3)H,N(1)H}$=1.8 Hz, $N_{(3)}H$), 8.38 (1H, dd, $^3J_{N(1)H,6\text{-}H}$=5.0, $^4J_{N(1)H,N(3)H}$=1.8 Hz, $N_{(1)}H$), 7.70–7.75 (2H, m, AA′ part of AA′XX′ spin system, $C_{(2)}H$ and $C_{(6)}H$ in 4-MeC_6H_4), 7.41–7.47 (2H, m, XX′ part of AA′XX′ spin system, $C_{(3)}H$ and $C_{(5)}H$ in 4-MeC_6H_4), 4.71 (1H, s, CH in H_2C=), 4.38 (1H, br s, 5-H), 4.08 (1H, s, CH in H_2C=), 3.78–3.86 (1H, m, 6-H), 2.42 (3H, s, CH_3 in Ts), 1.25–1.50 (2H, m, CH_2 in Et), 0.83 (3H, t, $^3J_{CH3,CH2}$=7.4 Hz, CH_3 in Et). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 154.01 ($C_{(2)}$), 144.93 ($C_{(4)}$ in 4-MeC_6H_4), 133.64 ($C_{(1)}$ in 4-MeC_6H_4), 130.50 ($C_{(4)}$), 129.57 ($C_{(3)}$ and $C_{(5)}$ in 4-MeC_6H_4), 129.00 ($C_{(2)}$ and $C_{(6)}$ in 4-MeC_6H_4), 117.07 (C≡N), 100.17 (=CH_2), 63.47 ($C_{(5)}$), 48.51 ($C_{(6)}$), 28.06 (CH_2 in Et), 21.18 (CH_3 in Ts), 9.59 (CH_3 in Et).
9. Spectral characteristics of **13b**: ^1H NMR (300.13 MHz, DMSO-d_6) δ: 9.89 (1H, d, $^4J_{N(3)H,N(1)H}$=1.8 Hz, $N_{(3)}H$), 8.38 (1H, dd, $^3J_{N(1)H,6\text{-}H}$=5.0, $^4J_{N(1)H,N(3)H}$=1.8 Hz, $N_{(1)}H$), 4.72 (1H, s, CH in H_2C=), 4.35 (1H, br s, 5-H), 4.08 (1H, s, CH in H_2C=), 3.88–3.96 (1H, m, 6-H), 2.42 (3H, s, CH_3 in Ts). Signals of other protons overlap with proton signals of compounds **7b**, **8b** and **11b**.
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13. Similarly, compound **7a** was obtained by using MeCN as a solvent at rt for 7.7 h (Table 1, entry 3).
14. Crystallization of compounds **7** was performed as quickly as possible using previously heated solvent to prevent the formation of dehydration products **8**, **11** and **13**.
15. Similarly, compound **7b** was obtained by using MeCN as a solvent at rt (Table 1, entries 8–10).
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