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A New Convenient Synthesis of 5-Acyl-1,2,3,4-tetrahydropyrimidine-2-thiones/ones

Anatoly D. Shutalev*, Ekaterina A. Kishko, Natalie V. Sivova and Aleksei Yu. Kuznetsov

Department of Organic Chemistry, State Academy of Fine Chemical Technology, Vernadsky Ave. 86, Moscow 117571, Russian Federation, FAX +7-095-431-6332 (shutalev@orc.ru)

Abstract: An efficient one-pot synthesis of 5-acyl-1,2,3,4-tetrahydropyrimidine-2-thiones/ones is described. The synthesis is based on the reaction of readily available -tosyl substituted thioureas or ureas with enolates of -oxoesters or 1,3-dicarbonyl compounds followed by acid-catalyzed dehydration of the obtained 5-acyl-4-hydroxyhexahydropyrimidine-2-thiones/ones.

Keywords: -Tosyl substituted (thio)ureas, 5-acyl-1,2,3,4-tetrahydropyrimidine-2-thiones/ones.

Introduction

In recent years 5-acyl-1,2,3,4-tetrahydropyrimidine-2-thiones/ones ("Biginelli compounds", i.e., **5a-h**) received significant attention owing to their diverse range of biological properties. For example, some of these compounds are very potent calcium channel blockers [1]. The presence of several interacting functional groups in Biginelli compounds also determines their great synthetic potential [2].

At the present time there are a few general methods for the synthesis of 5-acyl-1,2,3,4-tetrahydropyrimidine-2-thiones/ones. One of them is the Biginelli reaction [2,3]. This very simple method involves acid-catalyzed three-component condensation of (thio)ureas, aldehydes and -oxoesters or 1,3-dicarbonyl compounds. The main disadvantage of this synthesis is quite often low yields of the desired pyrimidines because various side reactions occur. For instance, the reaction of urea and ethyl acetoacetate with aliphatic aldehydes gives ethyl 4-alkyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates in yields

less than 30-40 % [4]. A very attractive approach to the synthesis of Biginelli compounds has been developed by Atwal and co-workers [5]. This approach is based on the reaction of -arylidene- -oxoesters with S-(4-methoxybenzyl)isothiourea or O-methylisourea in the presence of sodium bicarbonate followed by transformation of the obtained 2-(4-methoxybenzylthio)- or 2-methoxy-1,4-dihydropyrimidine-5-carboxylates into 2-thioxo- or 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates.

Recently we have demonstrated [6,7] that Biginelli compounds can be easily prepared by reaction of -azido or -tosyl substituted thioureas and ureas with sodium enolates of -oxoesters or 1,3-dicarbonyl compounds followed by acid-catalyzed dehydration of the obtained 5-acyl-4-hydroxyhexahydropyrimidine-2-thiones/ones. Both these stages of synthesis proceed under mild conditions and usually in high yields. This method is very flexible and makes it possible to prepare a large number of 1,2,3,4-tetrahydropyrimidine-2-thiones/ones bearing various substituents in the pyrimidine ring.

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* To whom correspondence should be addressed.

Continuing our work in this area we have developed an improved one-pot procedure for the synthesis of 5-acyl-1,2,3,4-tetrahydropyrimidine-2-thiones/ones, starting from -tosyl substituted thioureas and ureas without isolation of the intermediate 4-hydroxyhexahydropyrimidine-2-thiones/ones. In the present paper we report some preliminary results of the investigation.

Results and Discussion

The -tosyl substituted thioureas **1a-c** and ureas **1d,e** were chosen as starting compounds for the present investigation. These compounds were conveniently prepared in 1-2 steps from thiourea or urea in good yields using two different procedures (Scheme 1).
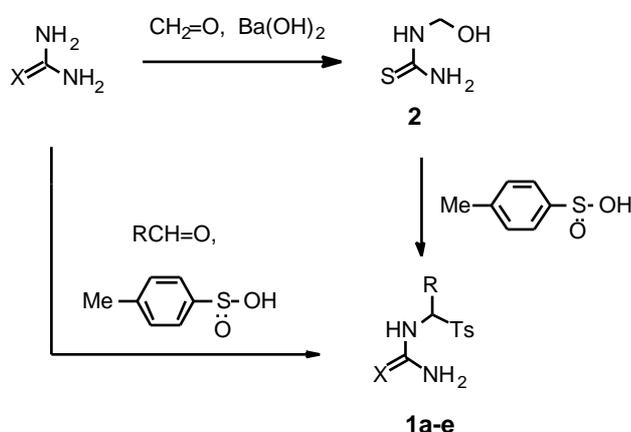
Scheme 1. Synthesis of -tosyl substituted thioureas **1a-c** and ureas **1d,e**.

N-(Tosylmethyl)thiourea **1a** was synthesized by reaction of readily available hydroxymethylthiourea **2** with *p*-toluenesulfinic acid in water (r.t., 24 h) in 94 % yield.

For the synthesis of -substituted *N*-(tosylmethyl)-thioureas and ureas we used methods based on a three-component condensation of thiourea or urea with aldehydes and *p*-toluenesulfinic acid. The main problem of the synthesis was the formation not only of the desired *N*-monosubstituted (thio)ureas of the type **1** but also of *N,N'*-disubstituted products. We showed that the amount of the latter depends on the molar ratio of the reagents, reaction conditions and the solvent [8]. Thus *N*-(1-tosyl-propyl)thiourea **1b** and *N*-(-tosylbenzyl)thiourea **1c** were synthesized by treatment of thiourea with *p*-toluenesulfinic acid and propionic aldehyde or benzaldehyde in water at r.t. for 21 h in good yields using an equimolar ratio of the reagents (Table 1). According to NMR spectra of the obtained products, the corresponding *N,N'*-bis(1-tosylpropyl)thiourea and *N,N'*-bis(-tosylbenzyl)thiourea were also formed as by-products in these reactions.

However, the amount of these disubstituted thioureas in relation to the monosubstituted products **1b,c** under the above conditions was only 1-2.5 mol%.

We found that the reaction of urea with *p*-toluenesulfinic acid and propionic aldehyde or benzaldehyde in water afforded significantly more *N,N'*-bis-products than in the case of thiourea under the described above conditions. In order to decrease the formation of the bis-products we used a three-fold molar excess of urea and a short reaction time (2 h). Thus we prepared *N*-(1-tosylpropyl)urea **1d** and *N*-(-tosylbenzyl)urea **1e** in 85-90 % yields. According to NMR spectra, the amount of *N,N'*-bis(1-tosylpropyl)urea and *N,N'*-bis(-tosylbenzyl)urea in relation to the compounds **1d,e** was 5.5 mol% and less than 1 mol%, respectively. The obtained -tosyl substituted (thio)ureas **1a-e** owing to their good purity (> 94 %) were used in the pyrimidine synthesis without further purification.

Table 1. Synthesis of -tosyl substituted thioureas **1a-c** and ureas **1d,e**.

Product	X	R	Yield, %
1a	S	H	94
1b	S	Et	95
1c	S	Ph	83
1d	O	Et	85
1e	O	Ph	90

It should be noted, that earlier Engberts and co-workers demonstrated [9] that the reaction of thiourea or urea with benzaldehyde and sodium *p*-toluenesulfinate in the presence of an excess of formic acid (water-ethanol, r.t.) gave, respectively, a mixture of **1c** and *N,N'*-bis(-tosylbenzyl)thiourea or a mixture of **1e** (37 %) and *N,N'*-bis(-tosylbenzyl)urea (43 %). The authors were only able to isolate a **1c** from these mixtures.

As a second building block for the pyrimidine synthesis in the present work we used -oxoesters **3a,b** or 1,3-dicarbonyl compounds **3c,d**.

For the first time we studied the reaction of the thioureas **1a-c** with the sodium enolate of ethyl acetoacetate obtained previously from **3a** or generated *in situ* by treatment of **3a** with NaH in acetonitrile. We found that the reaction of **1a** with the sodium enolate of **3a** (1.15 equiv.) easily proceeded in acetonitrile at r.t. for 3 h to afford 4-hydroxyhexahydropyrimidine-2-thione **4a** which was dehydrated after the addition of TsOH (0.3 equiv.) followed by refluxing of the reaction mixture for
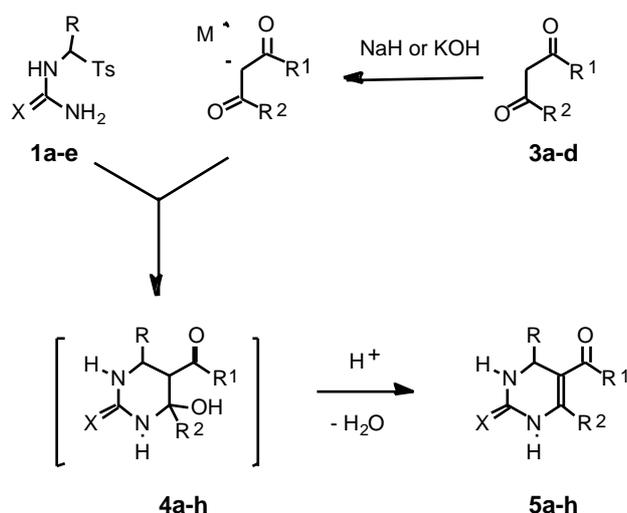
Scheme 2. Synthesis of 5-acyl-1,2,3,4-tetrahydropyrimidine-2-thiones/ones.

1.5 h. Thus we obtained the target 1,2,3,4-tetrahydro-pyrimidine-2-thione **5a** in 86 % yield and in a spectroscopically and TLC pure form (Method A) (Scheme 2). It should be noted that a workable catalyst for the dehydration is *p*-toluenesulfinic acid which is generated by the reaction of TsOH with sodium *p*-toluenesulfinate obtained in the first stage of the synthesis.

Similarly, the thioureas **1b,c** reacted with the sodium enolate of **3a** in acetonitrile (r.t., 3 h for **1b** and r.t., 3h, then reflux, 2 h for **1c**) to produce the hydroxypyrimidines **4e,f** which without their isolation were dehydrated into 1,2,3,4-tetrahydropyrimidine-2-thiones **5e,f** in 74-86% yields after addition of TsOH to the reaction mixtures (reflux, 1.5 h).

The described approach was also applied to the one-pot synthesis of 1,2,3,4-tetrahydropyrimidine-2-ones **5g,h** by reaction of the ureas **1d,e** with the sodium enolate of **3a** in acetonitrile followed by acidification and refluxing of the reaction mixtures. The yield of the pyrimidines **5g,h** was 73 and 65 %, correspondingly (Table 2).

We also found that for the pyrimidine synthesis potassium hydroxide in ethanol can be effectively used for generation of enolates from CH acids **3a-d** instead of NaH in acetonitrile. Thus reaction of the tosylthiourea **1a** with the potassium enolates of **3a-d** (1.2 equiv. for **3a,c** and 1.05 equiv. for **3b,d**) obtained by treatment of **3a-d** with KOH in ethanol afforded (r.t., 4.5 h) the corresponding hydroxypyrimidine-2-thiones **4a-d** which were dehydrated after addition of TsOH (0.27 equiv. for **4a,c,d** and 1.08 equiv. for **4b**) and refluxing of the reaction mixtures for 1.5 h to give the tetrahydropyrimidine-2-thiones **5a-d** in 71-87% yields (Table 2) (Method B). Analogously, we prepared the pyrimidine **5e** starting from **1b** and **3a** in 77 % yield.

Table 2. Synthesis of 5-acyl-1,2,3,4-tetrahydropyrimidine-2-thiones/ones **5a-h**.

Starting compounds		Product	X	R	R^1	R^2	Yield, % (Method)	Literature yields, %
1a	**3a**	**5a**	S	H	OEt	Me	86 (A), 87 (B)	58[b] [6], 68[c] [6]
1a	**3b**	**5b**	S	H	OEt	Ph	71[a] (B)	63[b] [6]
1a	**3c**	**5c**	S	H	Me	Me	74 (B)	41[b] [6], 52[c] [6]
1a	**3d**	**5d**	S	H	Ph	Me	74[a] (B)	55[b] [6]
1b	**3a**	**5e**	S	Et	OEt	Me	74 (A), 77 (B)	34[b] [7]
1c	**3a**	**5f**	S	Ph	OEt	Me	86 (A)	69[b] [7], 76 [10]
1d	**3a**	**5g**	O	Et	OEt	Me	73 (A)	38 [4], 15 [11]
1e	**3a**	**5h**	O	Ph	OEt	Me	65 (A)	73 [4], 40 [11], 79 [12]

[a] After washing of the crude product with a small portion of cold diethyl ether (-15 °C). [b] Overall yield for two stages from the corresponding thioureas **1a-c**. [c] Overall yield for two stages from *N*-(azidomethyl)thiourea.

A comparison of Method A and Method B shows that, even though both methods give similar yields of the target pyrimidines (Table 2), Method B is preparatively more convenient.

Conclusion

Thus the present work demonstrates that 5-acyl-1,2,3,4-tetrahydropyrimidine-2-thiones/ones ("Biginelli compounds") can be efficiently prepared by a one-pot reaction of readily available -tosyl substituted thioureas or ureas with enolates of -oxoesters or 1,3-dicarbonyl compounds followed by an acid treatment of the reaction mixtures. The application of this method provides a simple powerful tool for the synthesis of a large number of multi-functional pyrimidine-2-thiones/ ones. Mild reaction conditions, good overall yields, and flexibility make the described method very attractive.

Experimental

General

IR spectra (in Nujol) were recorded on a Shimadzu IR 435 spectrophotometer. Peak intensities in the IR spectra are defined as strong (s), medium (m) or weak (w). UV spectra (in methanol) were obtained on a Beckman DU 6 spectrophotometer. ^{1}H NMR (200.13 MHz) spectra were recorded on a Bruker MSL 200 spectrometer using DMSO-d_6 or CDCl$_3$ as solvents. Chemical shifts ( ) are given in ppm relative to TMS. 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 vapor or UV light.

p-Toluenesulfinic acid was synthesized by reduction of tosyl chloride with sodium sulfite in water [13], dried over P$_2$O$_5$ and stored at 0°C. Hydroxymethylthiourea **2** was prepared according to the literature procedure [14]. Propionic aldehyde and benzaldehyde were distilled before use. For the pyrimidine synthesis we used commercially available ethanol (96 %) and anhydrous acetonitrile dried by distillation from P$_2$O$_5$ and then from CaH$_2$. Ethyl acetoacetate and acetylacetone were dried over CaCl$_2$ and distilled under vacuum, ethyl benzoylacetate and benzoylacetone were commercially available products. Sodium hydride (80 % suspension in mineral oil) was washed with dry hexane, dried in vacuum desiccator prior to use. The sodium enolate of ethyl acetoacetate was obtained by reaction of ethyl acetoacetate with NaH in dry acetonitrile followed by filtration of the resulting product. -Tosyl substituted (thio)ureas **1a-e** were used in the syntheses freshly prepared because these compounds (especially **1b-e**) decomposed slightly during prolonged storage.

The obtained tetrahydropyrimidine-2-thiones/ones **5a-h** were identical (TLC, IR, ^{1}H NMR) with authentic samples prepared according to the literature procedures [4,6,7]. All yields refer to isolated, spectroscopically and TLC pure material.

N-(Tosylmethyl)thiourea (*1a*)

A mixture of hydroxymethylthiourea **2** (1.356 g, 12.77 mmol) and *p*-toluenesulfinic acid (2.399 g, 15.36 mmol) in 15 mL of water was stirred at r.t. for 24 h, then cooled to 0 °C. The solid was collected by filtration, washed carefully with ice water, hexane and dried to give 2.943 g (94 %) of **1a** as a white powder. The obtained product was used in the pyrimidine syntheses without further purification. Analytically pure material was obtained by recrystallisation from acetone, mp 156.5-157 °C.

IR 3392 br m, 3291 br s, 3180 br m, 3077 w, 3041 w, 1608 s, 1548 s, 1271 s, 1133 s, 802 m cm^{-1}.

^{1}H NMR (DMSO-d_6) 2.41 (3H, s, CH$_3$), 5.13 (2H, br d, *J* ~ 6 Hz, CH$_2$), 7.08-7.75 (2H, NH$_2$, the signals are covered under H$_{arom}$), 7.43 (2H, d, *J* = 8.3 Hz, H$_{arom}$), 7.71 (2H, d, *J* = 8.3 Hz, H$_{arom}$), 8.30 (1H, br t, *J* ~ 6 Hz, NH).

Anal. Calcd for C$_9$H$_{12}$N$_2$O$_2$S$_2$: C, 44.22; H, 4.95; N, 11.51. Found: C, 44.19; H, 4.96; N, 11.62.

N-(1-Tosylpropyl)thiourea (*1b*)

To a mixture of propionic aldehyde (0.519 g, 8.94 mmol) and water (7 mL) was added thiourea (0.648 g, 8.51 mmol) and then *p*-toluenesulfinic acid (1.397 g, 8.94 mmol). The resulting suspension was stirred at r.t. for 21 h, cooled to 0 °C, the solid was collected by filtration, washed carefully with ice water, hexane and dried to give 2.192 g (95 %) of **1b** as a white solid. According to the NMR spectrum, the crude product also contained about 1 mol% of *N,N'*-bis(1-tosylpropyl)thiourea. The obtained product was stored at 0°C and used in the pyrimidine syntheses without further purification. Analytically pure material was obtained by recrystallisation from acetonitrile, mp 123.5-124.5 °C dec.

IR 3413 br s, 3315 br s, 3185 br s, 3044 br s, 1606 s, 1570 s, 1492 w, 1301 s, 1139 s, 808 m cm^{-1}.

^{1}H NMR (DMSO-d_6) 0.93 (3H, t, *J* = 7.3 Hz, CH$_2$*CH$_3$*), 1.69 (1H, m, *J* = 14.0, 10.2, 7.3 Hz, *CH$_2$*CH$_3$), 2.08 (1H, m, *J* = 14.0, 7.3, 3.3 Hz, *CH$_2$*CH$_3$), 2.39 (3H, s, CH$_3$), 5.71 (1H, dt, *J* = 10.2, 10.2, 3.3 Hz, N-CH), 6.98 (1H, br s, NH$_2$), 7.41 (2H, d, *J* = 8.1 Hz, H$_{arom}$), 7.68 (2H, d, *J* = 8.1 Hz, H$_{arom}$), 7.72 (1H, br s, NH$_2$), 8.33 (1H, d, *J* = 10.2 Hz, NH).

Anal. Calcd for C$_{11}$H$_{16}$N$_2$O$_2$S$_2$: C, 48.51; H, 5.92; N, 10.29. Found: C, 48.61; H, 5.93; N, 10.41.

N-(α-Tosylbenzyl)thiourea (*1c*)

This compound (2.750 g, 83 %) was obtained as a white powder by the reaction of thiourea (0.786 g, 10.32 mmol), benzaldehyde (1.095 g, 10.32 mmol) and *p*-

toluenesulfinic acid (1.612 g, 10.32 mmol) in 8 mL of water according to the procedure described for **1b**. According to the NMR spectrum, the crude product also contained 2.5 mol% of *N,N'*-bis(-tosylbenzyl)thiourea. The obtained product was stored at 0 °C and used in the pyrimidine syntheses without further purification. Analytically pure material was obtained by recrystallisation from acetonitrile, mp 139.5-140.5 °C (lit. mp 153-154 °C (ethanol) [9]).

IR 3347 br m, 3270 br s, 3168 br m, 1609 s, 1530 s, 1493 w, 1285 s, 1135 s, 802 s, 736 s, 697 s cm^{-1}.

^{1}H NMR (DMSO-d_6) 2.40 (3H, s, CH$_3$), 6.89 (1H, d, *J* = 10.5 Hz, N-CH), 7.43 (2H, d, *J* = 8.1 Hz, H$_{arom}$), 7.73 (2H, d, *J* = 8.1 Hz, H$_{arom}$), 6.95-8.00 (5H, m, C$_6$H$_5$), ~ 7.08 (1H, br s, NH$_2$), ~ 7.87 (1H, br s, NH$_2$), 9.14 (1H, d, *J* = 10.5 Hz, NH).

Anal. Calcd for C$_{15}$H$_{16}$N$_2$O$_2$S$_2$: C, 56.23; H, 5.03; N, 8.74. Found: C, 55.86; H, 4.98; N, 8.98.

*N-(1-Tosylpropyl)urea (**1d**)*

To a mixture of propionic aldehyde (2.124 g, 36.57 mmol) and water (40 mL) was added *p*-toluenesulfinic acid (5.719 g, 36.61 mmol) followed by the addition of urea (6.594 g, 109.80 mmol). The resulting suspension was stirred at r.t. for 2 h, cooled to 0 °C, the solid was filtered, washed with ice water, hexane and dried to yield 7.942 g (85 %) of **1d** as a white powder. According to the NMR spectrum, the crude product also contained 5.5 mol% of *N,N'*-bis(1-tosylpropyl)urea. The obtained product was stored at 0 °C and used in the pyrimidine syntheses without further purification.

IR 3415 s, 3381 m, 3191 br s, 1676 s, 1622 m, 1596 m, 1518 s, 1279 s, 1133 s, 811 m cm^{-1}.

^{1}H NMR (DMSO-d_6) 0.91 (3H, t, *J* = 7.3 Hz, CH$_2$*CH$_3$*), 1.54 (1H, m, *J* = 13.8, 10.5, 7.3 Hz, *CH$_2$*CH$_3$), 2.01 (1H, m, *J* = 13.8, 7.3, 3.4 Hz, *CH$_2$*CH$_3$), 2.39 (3H, s, CH$_3$), 4.81 (1H, dt, *J* = 10.3, 10.5, 3.4 Hz, N-CH), 5.65 (2H, br s, NH$_2$), 6.84 (1H, d, *J* = 10.3 Hz, NH), 7.40 (2H, d, *J* = 8.2 Hz, H$_{arom}$), 7.68 (2H, d, *J* = 8.2 Hz, H$_{arom}$).

*N-(α-Tosylbenzyl)urea (**1e**)*

This compound (10.611 g, 90 %) was obtained as a white powder by the reaction of urea (6.995 g, 116.48 mmol), benzaldehyde (4.119 g, 38.81 mmol) and *p*-toluenesulfinic acid (6.074 g, 38.88 mmol) in 40 mL of water according to the procedure described for **1d**. According to the NMR spectrum, the crude product contained less than 1 mol% of *N,N'*-bis(-tosylbenzyl)urea. The obtained product was stored at 0 °C and used in the pyrimidine syntheses without further purification.

IR 3465 br m, 3338 br s, 3180 br m, 1667 s, 1595 s, 1533 s, 1493 w, 1283 s, 1142 s, 812 m, 692 m cm^{-1}.

^{1}H NMR (DMSO-d_6) 2.40 (3H, s, CH$_3$), 5.77 (2H, br s, NH$_2$), 6.10 (1H, d, *J* = 10.6 Hz, N-CH), 7.41 (2H, d, *J* = 8.1 Hz, H$_{arom}$), 7.70 (2H, d, *J* = 8.1 Hz, H$_{arom}$), 7.30-7.82 (5H, m, C$_6$H$_5$), 7.73 (1H, d, *J* = 10.6 Hz, NH).

5-Acyl-1,2,3,4-tetrahydropyrimidine-2-thiones/ones;
General Procedures

Method A

To a stirred suspension of NaH (0.257 g, 10.71 mmol) in dry acetonitrile (10 mL) at 0 °C was added a solution of ethyl acetoacetate **3a** (1.394 g, 10.71 mmol) in dry acetonitrile (10 mL) dropwise over a period of 5 min and the resulting mixture was stirred at r.t. for 30 min. To the obtained suspension of the sodium enolate of ethyl acetoacetate was added the appropriate (thio)urea **1** (9.31 mmol) all at once. After stirring for 3 h at r.t. (for **1a,b,d**) or for 3 h at r.t. and then 2 h under reflux (for **1c,e**), the reaction mixture was acidified by addition of TsOH·H$_2$O (0.532 g, 2.80 mmol) and refluxed for 1.5 h. The solvent was removed under reduced pressure and the solid residue was treated with water (10 mL). The mixture was cooled to 0 °C over 1 h, the precipitate was filtered, washed carefully with ice water, hexane and dried to give the corresponding pyrimidine **5** (Table 2).

Analogously and in similar yields the pyrimidines **5a,e-h** were also obtained by modification of Method A based on the reaction of an appropriate (thio)urea **1** (3.71 mmol) with the previously prepared sodium enolate of ethyl acetoacetate (0.648 g, 4.26 mmol) in acetonitrile (18 mL) followed by addition of TsOH·H$_2$O (0.285 g, 1.50 mmol).

Method B

To a stirred solution of KOH (0.308 g, 5.49 mmol) in ethanol (10 mL) was added a solution of CH acid **3** (5.49 mmol for **3a,c** or 4.81 mmol for **3b,d**) in ethanol (15 mL) at r.t. in one portion and the resulting mixture was stirred for 15 min. Tosylthiourea **1a** or **1b** (4.58 mmol) was added all at once. After stirring for 4.5 h at r.t., the reaction mixture was acidified by addition of TsOH·H$_2$O (0.235 g, 1.24 mmol in the case of **3a,c,d** or 0.942 g, 4.95 mmol in the case of **3b**) and refluxed for 1.5 h. The solvent was removed under reduced pressure and the solid residue was treated with water (5 mL). The mixture was cooled to 0 °C over 1 h, the precipitate was filtered, washed carefully with ice water, hexane and dried to give the corresponding pyrimidine **5** (Table 2).

*Ethyl 6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**5a**)*

Yield 86 % (Method A) and 87 % (Method B), colorless crystals, mp 236-237 °C dec (methanol).

IR 3194 br s, 3152 br s, 1716 s, 1662 s, 1615 s, 1595 m, 1505 s, 1274 s, 1205 s, 1104 s cm^{-1}.

UV $_{max}$ (log) 206 (4.11), ~280 sh, 306 nm (4.18).

^{1}H NMR (DMSO-d_6) 1.19 (3H, t, J = 6.9 Hz, OCH$_2$*CH$_3$*), 2.18 (3H, s, CH$_3$), 3.89 (2H, s, N-CH$_2$), 4.08 (2H, q, J = 6.9 Hz, O*CH$_2$*CH$_3$), 8.79 (1H, br s, NH), 9.78 (1H, br s, NH).

Anal. Calcd for C$_8$H$_{12}$N$_2$O$_2$S: C, 47.98; H, 6.04; N, 13.99; S, 16.01. Found: C, 47.73; H, 5.92; N, 14.01; S, 16.00.

Ethyl 6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5b)

The crude product (Method B) was washed with a small portion of cold diethyl ether (-15 ^{o}C), yield 71 %, pale yellow crystals, mp 196-197 ^{o}C (ethanol).

IR 3303 br m, 3174 br s, 1665 s, 1581 s, 1292 s, 1187 s, 1138 s, 760 s, 695 s cm^{-1}.

UV $_{max}$ (log) 208 (4.43), 244 sh, ~284 sh, 310 nm (4.19).

^{1}H NMR (CDCl$_3$) 0.92 (3H, t, J = 7.1 Hz, OCH$_2$*CH$_3$*), 3.93 (2H, q, J = 7.1 Hz, O*CH$_2$*CH$_3$), 4.26 (2H, d, J = 1.8 Hz, N-CH$_2$), 7.26-7.44 (5H, m, C$_6$H$_5$), 7.49 (1H, br s, NH), 7.75 (1H, br s, NH).

Anal. Calcd for C$_{13}$H$_{14}$N$_2$O$_2$S: C, 59.52; H, 5.38; N, 10.68; S, 12.22. Found: C, 59.03; H, 5.42; N, 10.48; S, 11.88.

5-Acetyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2-thione (5c)

Yield 74 % (Method B), colorless crystals, mp 230-230.5 ^{o}C dec (ethanol).

IR 3274 br s, 3180 br s, 3128 br s, 1647 sh, 1613 s, 1592 m, 1189 s, 1035 s cm^{-1}.

UV $_{max}$ (log) 207 (3.99), ~290 sh, 325 nm (4.19).

^{1}H NMR (DMSO-d_6) 2.17 (6H, s, CH$_3$ and CH$_3$C=O), 3.96 (2H, s, N-CH$_2$), 8.90 (1H, br s, NH), 9.88 (1H, br s, NH).

Anal. Calcd for C$_7$H$_{10}$N$_2$OS: C, 49.39; H, 5.92; N, 16.46. Found: C, 49.00; H, 5.82; N, 16.52.

5-Benzoyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2-thione (5d)

The crude product (Method B) was washed with a small portion of cold diethyl ether (-15 ^{o}C), yield 74 %, pale yellow crystals, mp 227.5-228 ^{o}C dec (ethanol).

IR 3282 br s, 3172 br s, 3108 br s, 1651 m, 1606 s, 1590 s, 1200 s, 732 m, 702 m cm^{-1}.

UV $_{max}$ (log) 207 (4.37), 253 (4.05), ~288 sh, 336 nm (4.22).

^{1}H NMR (DMSO-d_6) 1.72 (3H, s, CH$_3$), 3.91 (2H, s, N-CH$_2$), 7.40-7.60 (5H, m, C$_6$H$_5$), 8.97 (1H, br s, NH), 10.00 (1H, br s, NH).

Anal. Calcd for C$_{12}$H$_{12}$N$_2$OS: C, 62.05; H, 5.21; N, 12.06. Found: C, 62.00; H, 5.18; N, 12.22.

Ethyl 4-ethyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5e)

Yield 74 % (Method A) and 77 % (Method B), colorless crystals, mp 150.5-151.5 ^{o}C (ethanol).

IR 3316 br s, 3182 br s, 3109 br m, 1656 s, 1575 s, 1276 s, 1188 s, 1122 s cm^{-1}.

UV $_{max}$ (log) 207 (4.04), 304 nm (4.22).

^{1}H NMR (CDCl$_3$) 0.91 (3H, t, J = 7.5 Hz, CH$_2$*CH$_3$*), 1.27 (3H, t, J = 7.2 Hz, OCH$_2$*CH$_3$*), 1.45-1.72 (2H, m, *CH$_2$*CH$_3$), 2.30 (3H, s, CH$_3$), 4.16 (1H, dq, J = 11.0, 7.2 Hz, O*CH$_2$*CH$_3$), 4.19 (1H, dq, J = 11.0, 7.2 Hz, O*CH$_2$*CH$_3$), 4.32 (1H, ddd, N-CH), 7.60 (1H, br s, NH), 8.10 (1H, br s, NH).

Anal. Calcd for C$_{10}$H$_{16}$N$_2$O$_2$S: C, 52.61; H, 7.06; N, 12.27; S, 14.04. Found: C, 52.52; H, 7.15; N, 12.34; S, 13.90.

Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5f)

Yield 86 % (Method A), colorless crystals, mp 212-213 ^{o}C (ethanol) (lit. mp 207 ^{o}C (ethanol) [10]).

UV $_{max}$ (log) 209 (4.31), 308 nm (4.33).

IR 3324 br s, 3159 br s, 3088 br m, 1667 s, 1573 s, 1281 s, 1198 s, 1178 s, 1117 s, 758 s, 718 s, 688 s cm^{-1}.

^{1}H NMR (CDCl$_3$) 1.14 (3H, t, J = 7.2 Hz, OCH$_2$*CH$_3$*), 2.34 (3H, s, CH$_3$), 4.05 (1H, dq, J = 10.8, 7.2 Hz, O*CH$_2$*CH$_3$), 4.08 (1H, dq, J = 10.8, 7.2 Hz, O*CH$_2$*CH$_3$), 5.38 (1H, d, J = 3.2 Hz, N-CH), 7.22-7.37 (5H, m, C$_6$H$_5$), 7.86 (1H, br s, NH), 7.86 (1H, br s, NH).

Anal. Calcd for C$_{14}$H$_{16}$N$_2$O$_2$S: C, 60.85; H, 5.84; N, 10.14; S, 11.60. Found: C, 60.65; H, 5.84; N, 10.28; S, 11.36.

Ethyl 4-ethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5g)

Yield 73 % (Method A), colorless crystals, mp 184-185 ^{o}C (ethanol) (lit. mp 184-185 ^{o}C (ethanol)[11]).

IR 3248 br s, 3118 br s, 1730 s, 1706 s, 1676 s, 1647 s, 1285 s, 1237 s, 1119 s cm^{-1}.

^{1}H NMR (DMSO-d_6) 0.80 (3H, t, J = 7.3 Hz, CH$_2$*CH$_3$*), 1.19 (3H, t, J = 7.0 Hz, OCH$_2$*CH$_3$*), 1.43 (2H, m, *CH$_2$*CH$_3$), 2.17 (3H, s, CH$_3$), 3.99-4.10 (1H, m, N-CH, the signals are partly overlapped with OCH$_2$), 4.05 (1H, dq, J = 10.8, 7.0 Hz, O*CH$_2$*CH$_3$), 4.08 (1H, dq, J = 10.8, 7.0 Hz, O*CH$_2$*CH$_3$), 7.20 (1H, br s, NH), 8.84 (1H, br s, NH).

Anal. Calcd for C$_{10}$H$_{16}$N$_2$O$_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.72; H, 7.38; N, 13.27.

Ethyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5h)

Yield 65 % (Method A), colorless crystals, mp 212.5-213.5 ºC (ethanol) (lit. mp 203-204 ºC [11], 202-204 ºC [12], 206-208 ºC [15]).

IR 3228 br s, 3100 br s, 1728 s, 1702 s, 1645 s, 1600 w, 1287 s, 1226 s, 1091 s, 754 s, 695 s, cm^{-1}.

References and Notes

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8. Detailed investigation of reaction of (thio)ureas with aldehydes and arylsulfinic acid will be subject for one of our future publications.

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Sample Availability: Available from the authors.