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Synthesis of 5-R-thio, 5-R-sulfinyl, 5-R-sulfonyl and 5-di(R-oxy)phosphoryl substituted hydrogenated pyrimidine-2-thiones/ones

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Abstract: general and efficient synthesis of hexahydro- and 1,2,3,4-tetrahydropyrimidine-2-thiones/ones bearing R-thio, R-sulfinyl, R-sulfonyl and di(R-oxy)phosphoryl groups at the C(5) is described. The key stage of the synthesis is reaction of readily available a-tosyl or a-azido substituted thioureas or ureas with enolates of the corresponding a-substituted ketones.

Keywords: 5-R-thio, 5-R-sulfinyl, 5-R-sulfonyl, 5-di(R-oxy)phosphoryl substituted 4-hydroxyhexahydropyrimidine-2-thiones/ones and 1,2,3,4-tetrahydropyrimidine-2-thiones/ones, (thio)ureidoalkylation, a-tosyl and a-azido substituted (thio)ureas, functionally substituted ketones

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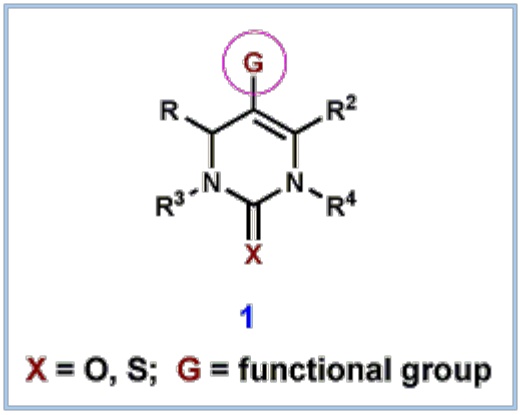
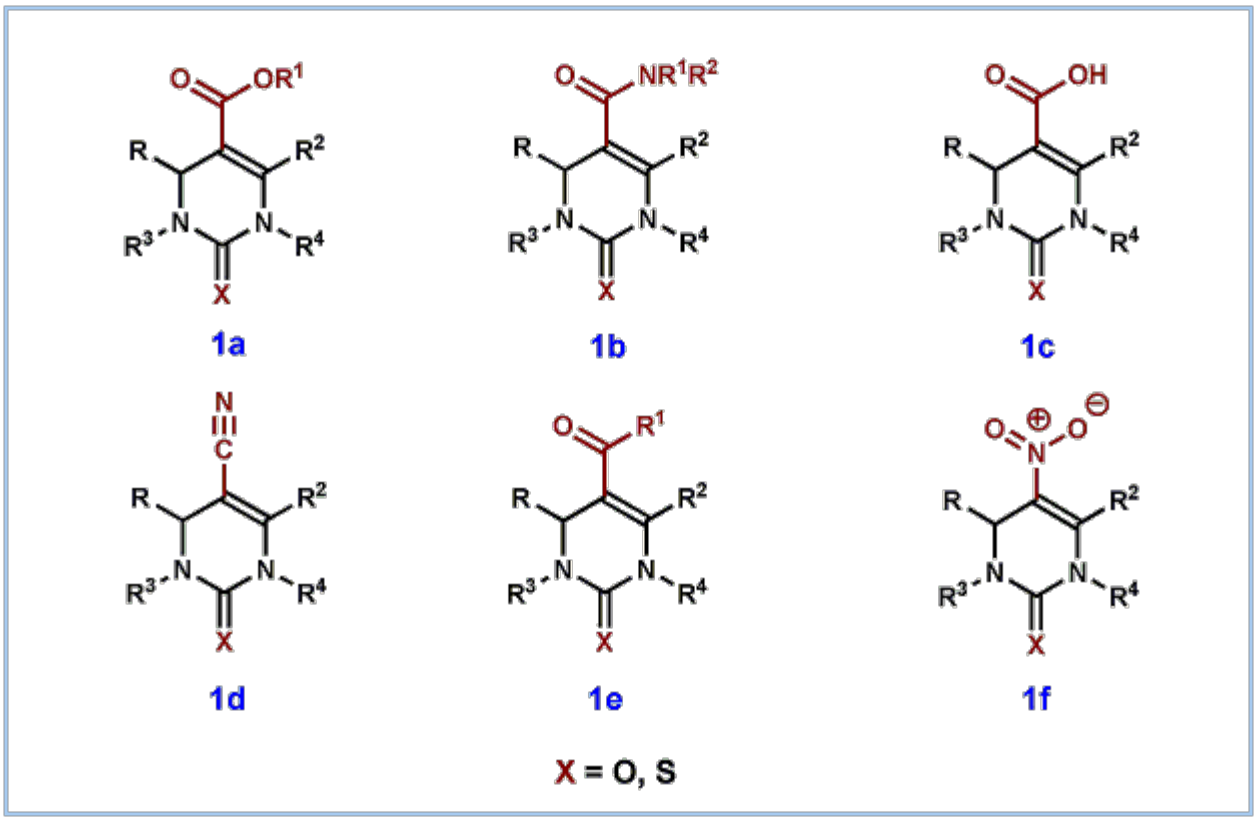
Introduction

5-Functionally substituted 1,2,3,4-tetrahydropyrimidin-2-ones and their 2-thioxo analogues (**1**) have attracted considerable interest in recent years.



Much of this interest has arisen from the multifaceted pharmacological profiles of such heterocycles. For example, esters of 4-aryl-2-oxo(or thioxo)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acids (**1a**; so-called "Biginelli compounds") have emerged as orally active antihypertensive agents [1, 2], mitotic kinesin Eg5 inhibitors [3], a_{1a} antagonists [4], etc.



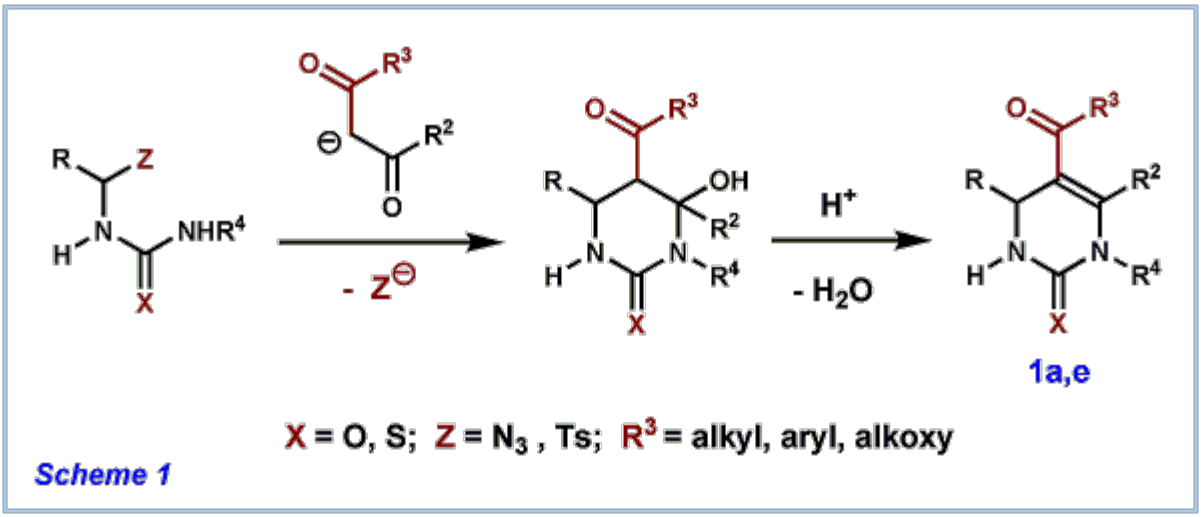
Besides **1a**, some other types of **1** particularly bearing carboxamido (**1b**) [5], carboxy (**1c**) [6], cyano (**1d**) [7], acyl (**1e**) [8], and nitro group (**1f**) [9] at the $C_{(5)}$ are also known. However, hitherto a lot of **1** (for example 5-R-thio, 5-R-sulfinyl, 5-R-sulfonyl, 5-di(R-oxy)phosphoryl

substituted ones) remain inaccessible and their biological activities are unexplored. This is because the lack of methods of these compounds preparation.

At the present time there are a few general methods of the synthesis of 1,2,3,4-tetrahydropyrimidine-2-thiones/ones, containing carboxylate, carboxamide and acyl groups at the $C_{(5)}$ (**1a,b,e**) from acyclic precursors. All three type of compounds can be prepared by the Biginelli reaction [10, 11]. This very simple method involves acid-catalyzed three-component condensation of (thio)ureas, aldehydes and b-oxoesters, b-oxoamides or 1,3-dicarbonyl compounds correspondingly. In the last decade various improvements of the classical Biginelli protocol were proposed [12-15].

Very attractive approach to the synthesis of Biginelli compounds (**1a**) was developed by Atwal and co-workers [16, 17]. This approach is based on the reaction of a-arylidene-b-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-carboxylate. The similar route giving access to 5-nitro substituted pyrimidin-2-ones (**1f**) was developed in works of Remennikov and co-workers [9, 18].

Recently we have developed a new approach to the synthesis of various 5-acyl-and 5-alkoxycarbonyl substituted pyrimidine-2-thiones/ones (**1a,e**) [19-21]. This approach is based on the reaction of a-azido or a-tosyl substituted thioureas and ureas with sodium enolates of b-oxoesters and 1,3-dicarbonyl compounds followed by acid-catalyzed dehydration of the obtained 4-hydroxyhexahydropyrimidine-2-thiones/ones (*Scheme 1*).



Scheme 1

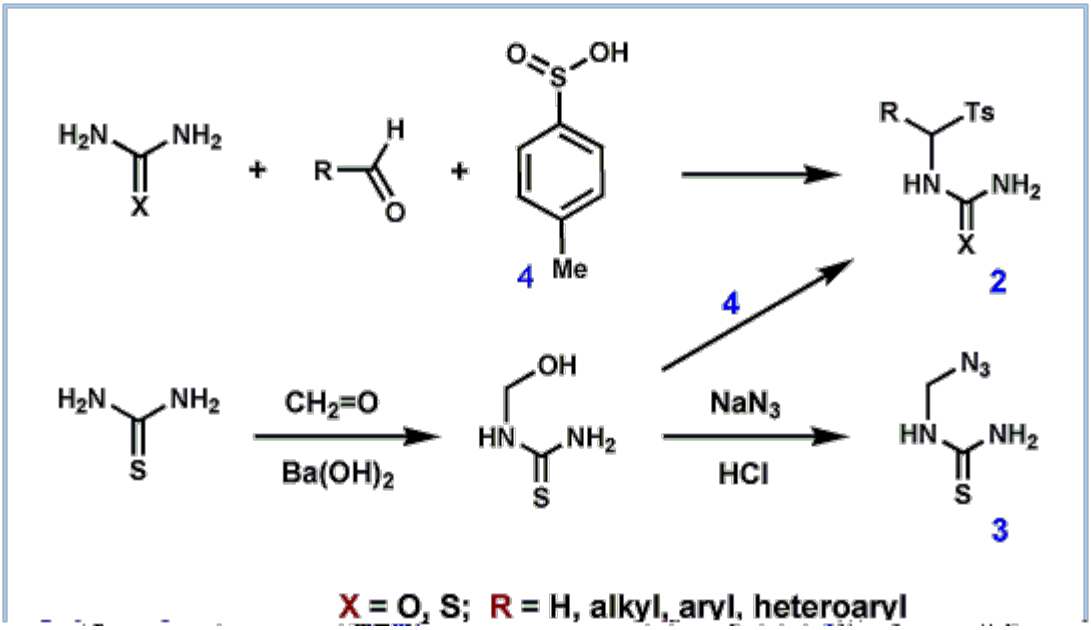
We found that our approach to the synthesis of **1a,e** is very flexible and permits a large variation of starting reagents structures. Thus, it is possible to prepare a large number of 1,2,3,4-tetrahydropyrimidine-2-thiones/ones **1a,e** bearing various substituents in pyrimidine ring (X, R, R_2, R_3 and R_4). We proposed that the described method could be applied not only to the synthesis of **1a,e** but also others 5-functionally substituted 1,2,3,4-tetrahydropyrimidine-2-thiones/ones (for example **1b,c,d,f**). In present communication we wish to report on

synthesis of 5-R-thio, 5-R-sulfinyl, 5-R-sulfonyl, 5-di(R-oxy)phosphoryl substituted hexahydro- and 1,2,3,4-tetrahydropyrimidine-2-thiones/ones which are representatives of earlier unknown types of functionalized pyrimidines.

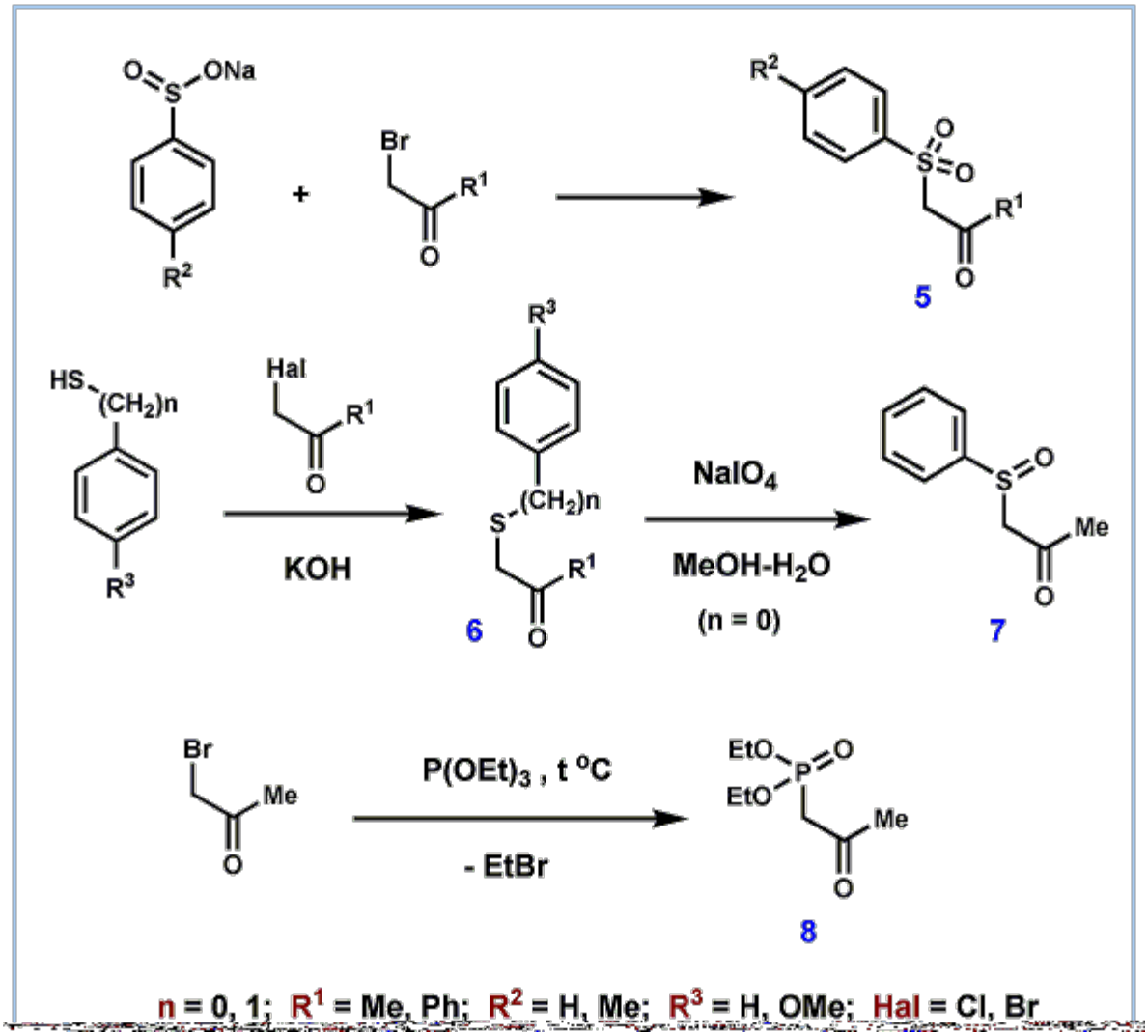
Results and Discussion

Synthesis of the starting compounds

The electrophilic (thio)ureidoalkylation reagents, namely a-tosyl substituted (thio)ureas **2** and N-(azidomethyl)thiourea **3**, were conveniently prepared in 1-2 steps from thiourea or urea in good yields using two different procedures (*Scheme 2*). One of them involved the direct reaction of (thio)ureas with aliphatic or aromatic aldehydes and *p*-toluenesulfinic acid (**4**) in water at 20 °C. This procedure gives access to a large number of tosyl substituted (thio)ureas **2** (R = alkyl, aryl). The other method was based on the reaction of thiourea with formaldehyde followed by the treatment of the obtained hydroxymethylthiourea with *p*-toluenesulfinic acid or hydrazoic acid in water at 20 °C. This route was suitable for the synthesis of N-(tosylmethyl)thiourea **2** (R = H) and N-(azidomethyl)thiourea **3**.

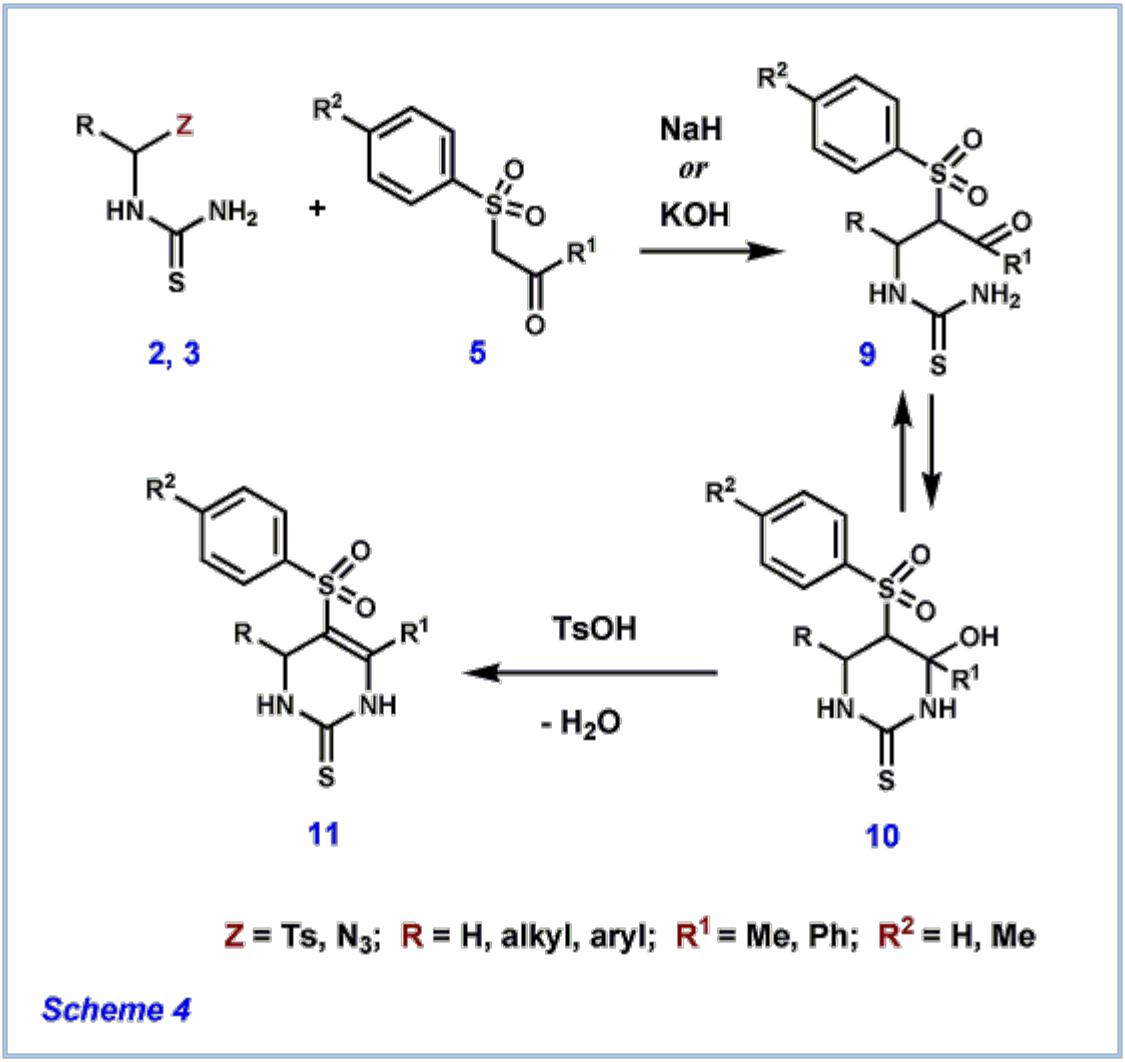


As a second building block for the pyrimidine synthesis in the present work we used various ketones bearing R-thio, R-sulfinyl, R-sulfonyl and di(R-oxy)phosphoryl groups at the a-position (**5-8**) which were prepared according to *Scheme 3*.



Synthesis of 5-R-sulfonyl substituted pyrimidine-2-thiones

We found that a-tosyl substituted thioureas **2** or N-(azidomethyl)thiourea (**3**) readily reacted with enolates of a-(arylsulfonyl)acetones generated by treatment of the corresponding *CH*-acids (**5** R_1 = Me) with NaH in acetonitrile or KOH in ethanol to produce the corresponding 5-arylsulfonyl-4-hydroxyhexahydropyrimidine-2-thiones (**10**) in good yields and high diastereoselectivity (*Scheme 4*). Clearly, the pyrimidines **10** are products of spontaneous heterocyclization of the intermediate N-[2-(arylsulfonyl)-3-oxopropyl]thioureas (**9** R_1 = Me). In contrast, the reaction of **2** or **3** with enolates of a-(arylsulfonyl)acetophenones (**5** R_1 = Ph) failed to give 5-arylsulfonyl-4-hydroxyhexahydropyrimidine-2-thiones (**10**). According to IR, ^{1}H and ^{13}C NMR spectral data, the obtained products were N-[2-(arylsulfonyl)-3-oxopropyl]thioureas (**9** R_1 = Ph), both in solid state and in solutions. This fact could be explained by scarce electrophilicity of carbonyl group of **9** (R_1 = Ph) as well as steric hindrances for heterocyclization into **10**.

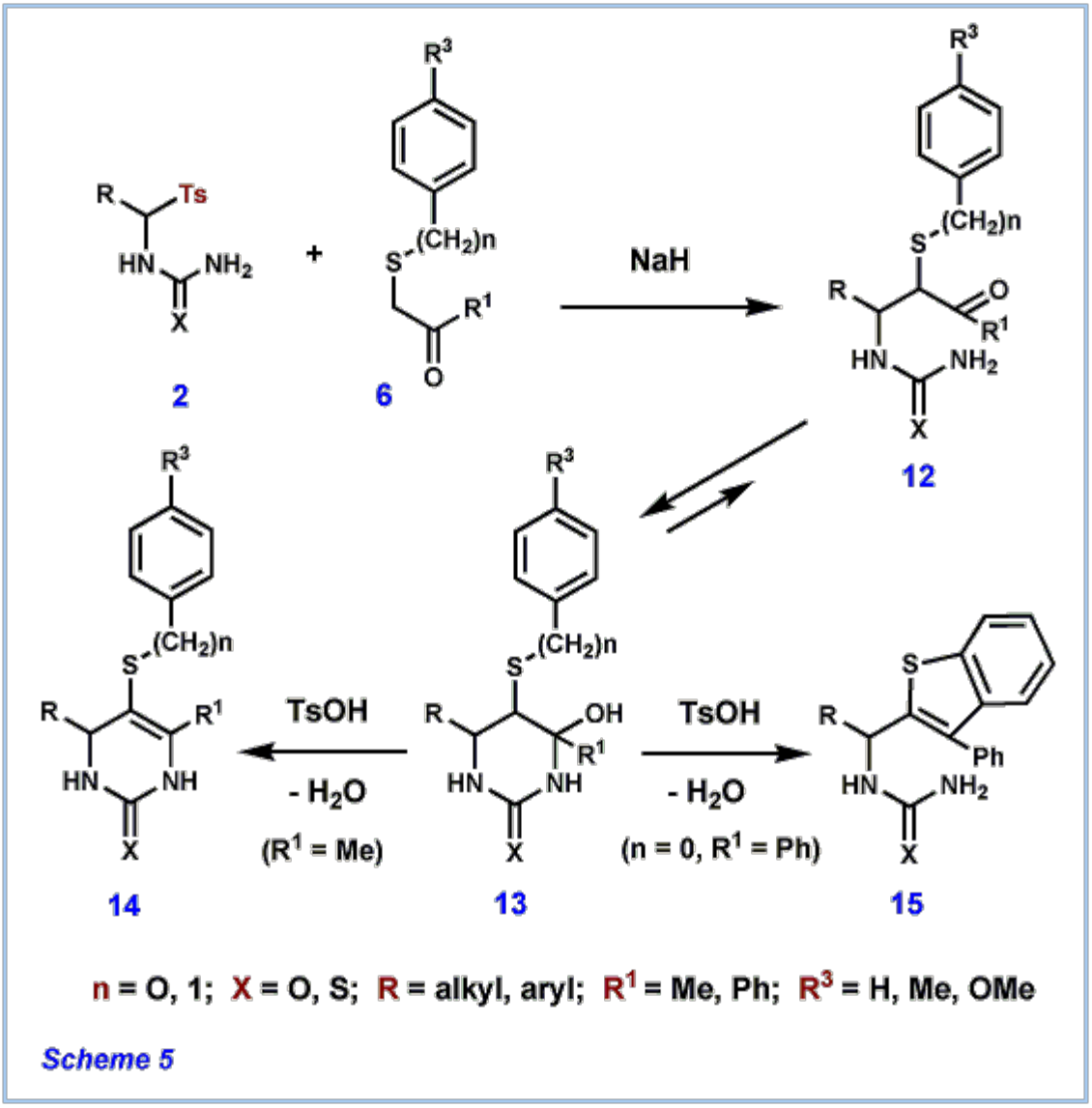


Scheme 4

The hydroxypyrimidines **10** (R_1 = Me) were dehydrated by refluxing in acetonitrile in the presence of *p*-toluenesulfonic acid (10 mol%) to furnish 5-arylsulfonyl-1,2,3,4-tetrahydropyrimidine-2-thiones (**11** R_1 = Me) in excellent yields. Dynamic equilibrium between **9** and **10** (R_1 = Ph) in solutions gave also possibility to convert **9** into **11** (R_1 = Ph). This reaction took place by refluxing **9** (R_1 = Ph) in acetonitrile in the presence of TsOH (> 50 mol%) in very good yields.

Synthesis of 5-R-thio substituted pyrimidine-2-thiones/ones

Next stage of our investigation concerned the reaction of a-substituted N-(tosylmethyl)thioureas and ureas **2** with a-phenylthio and a-benzylthio ketones **6**. We showed that this reaction readily proceeded in acetonitrile at 20 °C with the use of NaH as a base. In that way, the corresponding 5-phenylthio- and 5-benzylthio-4-hydroxyhexahydropyrimidine-2-thiones (**13**) were obtained in good yields and high diastereoselectivity (*Scheme 5*).



Scheme 5

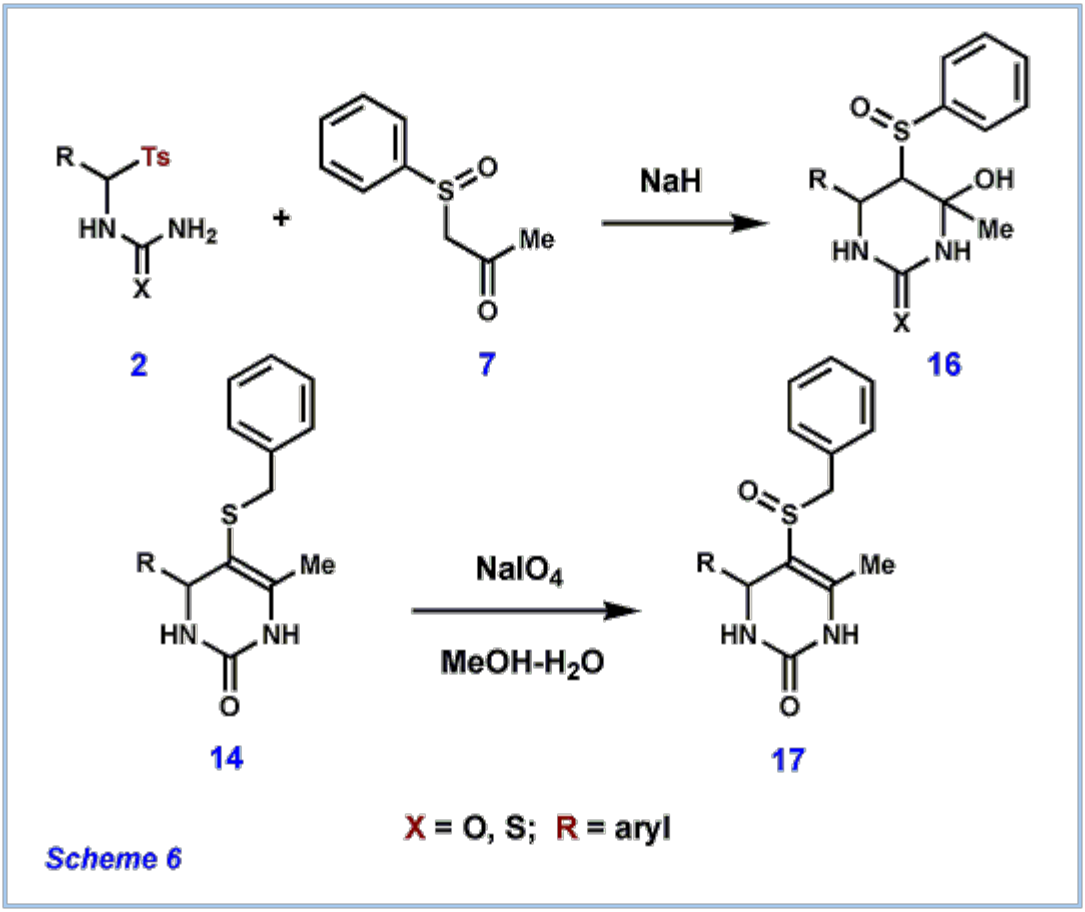
It should be noted that in contract to a-(arylsulfonyl)acetophenones (**5** R_1 = Ph) (see above), the reaction of a-(phenylthio)acetophenone (**6** n = 0, R_1 = Ph) with **2** gave only cyclic products **13** but not acyclic ones **12**.

The dehydration of 4-hydroxy-4-methyl-5-(R-thio)hexahydropyrimidine-2-thiones (**13** R_1 = Me) (30 mol% of TsOH, acetonitrile, reflux) led to formation of the expected 5-(R-thio)-1,2,3,4-tetrahydropyrimidine-2-thiones (**14** R_1 = Me). To the contrary, treatment of 4-hydroxy-4-phenylpyrimidines (**13** R_1 = Ph) with 1 equiv. of TsOH in boiling acetonitrile gave 2,3-disubstituted benzothiophenes **15** which were products of intramolecular electrophilic substitution in the acyclic isomeric forms of **13**, namely in **12**.

Synthesis of 5-R-sulfinyl substituted pyrimidine-2-thiones/ones

The described above method was applied also to the synthesis of hydrogenated pyrimidine-2-thiones/ones bearing phenylsulfinyl group at the $C_{(5)}$. Reaction of **2** with a-phenylsulfinylacetone **7** in the presence of NaH provided 4-hydroxy-5-phenylsulfinylpyrimidines

16 as mixtures of diastereomers (*Scheme 6*).

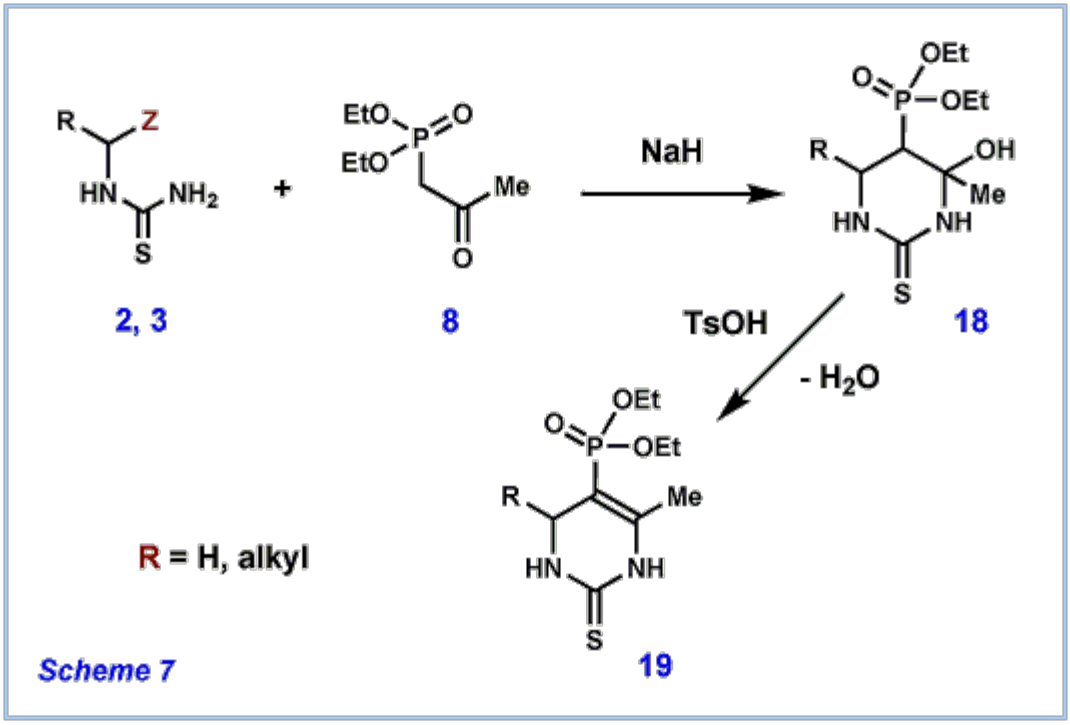


Scheme 6

5-Benzylsulfinyl-1,2,3,4-tetrahydropyrimidin-2-ones (**17**) were obtained by oxidation of the corresponding 5-benzylthiopyrimidines **14** with $NaIO_4$ in aqueous methanol.

Synthesis of 5-di(R-oxy)phosphoryl substituted pyrimidine-2-thiones

The final stage of our study was devoted to the reaction of a-substituted N-(tosylmethyl)thioureas **2** with sodium enolate of diethyl (2-oxopropyl)phosphonate (**8**). The products of this reaction, namely diethyl (4-hydroxy-2-thioxohexahydropyrimidin-5-yl)phosphonates (**18**) were dehydrated without their isolation in the presence of TsOH to give diethyl (2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)phosphonates (**19**) (*Scheme 7*).



Conclusion

Thus the present work demonstrates that earlier unknown 5-R-thio, 5-R-sulfinyl, 5-R-sulfonyl and 5-di(R-oxy)phosphoryl substituted 4-hydroxyhexahydropyrimidine-2-thiones/ones can be efficiently prepared by reaction of readily available a-tosyl or a-azido substituted thioureas or ureas with enolates of the corresponding a-substituted carbonyl compounds. Acid-catalized dehydration of the obtained products gives access to new types of 5-functionally substituted 1,2,3,4-tetrahydropyrimidine-2-thiones/ones. The application of this method provides a simple powerful tool for the synthesis of a large number of multifunctional pyrimidine-2-thiones/ones. Mild reaction conditions, good overall yields, flexibility make the described method very attractive.

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