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A NEW GENERAL APPROACH TO 5-FUNCTIONALIZED PYRIMIDINE-2-THIONES / ONES

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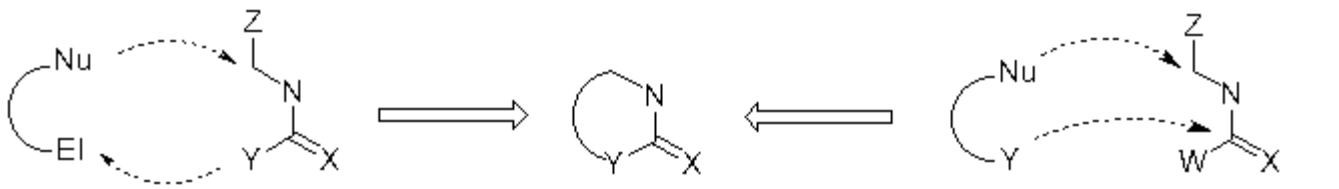
Abstract: A new general convenient approach to the synthesis of pyrimidine-2-thiones/ones has been developed. This approach is based on the preparation of a-tosyl and a-azido substituted thioureas and ureas followed by the reaction with sodium enolates of carbonyl compounds.

Keywords: Thioureas, ureas, aldehydes, p-toluenesulfinic acid, hydrazoic acid, amidoalkylation, C-H acids, hexahydropyrimidine-2-thiones/ones, 1,2,3,4-tetrahydropyrimidine-2-thiones/ones.

Introduction

Pyrimidine-2-thiones/ones, in particular partly or fully hydrogenated ones are an important class of heterocycles possessing a wide variety of biological activities [1] and high synthetic potential [2]. A large number of methods are available for the construction of these compounds from acyclic precursors [3]. Most of the methods include C-N bonds formation. However, there are only few examples of pyrimidine synthesis in which new C-C bonds are formed. In the course of our studies on hydrogenated nitrogen containing heterocycles and their glycosides [4], we have found that readily available cyclic thioureas, ureas, dithiocarbamates, etc. bearing arylsulfonyl or azido groups at the a-position to nitrogen are very efficient amidoalkylation reagents. We proposed that reactions of acyclic analogues of these compounds with suitable multifunctional C-nucleophiles could give general access to various heterocycles as outlined in scheme 1.

Scheme 1



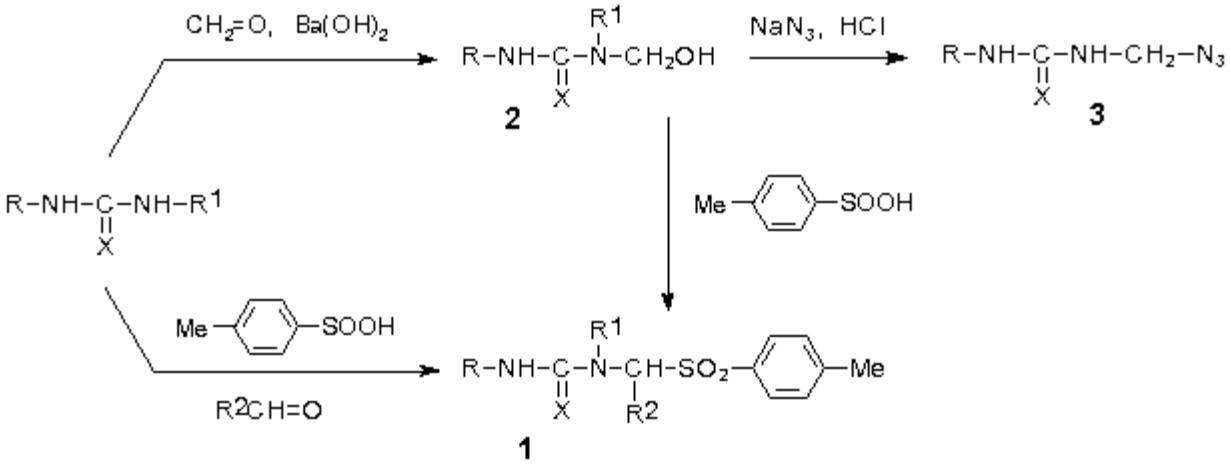
X = S, O; Y = N, S, O, C, etc.; Z, W = leaving groups.
Nu = C-nucleophilic center; El = C-electrophilic center.

Here we wish to report the preparation and usage of a-tosyl and a-azido substituted thioureas and ureas for new convenient synthesis of 5-functionalized hydrogenated pyrimidine-2-thiones/ones by (N-C-N-C + C-C) condensation *via* amidoalkylation.

Results and Discussion

We developed two methods for the preparation of the a-tosyl substituted thioureas and ureas **1** (Scheme 2). One of them is based on the reaction of thioureas or ureas with formaldehyde followed by the treatment of the obtained (hydroxymethyl)(thio)ureas **2** with p-toluenesulfinic acid in water at 20 °C. This route is suitable for the synthesis of (tosylmethyl)(thio)ureas **1** (R^2 = H). The other method involves the direct reaction of (thio)ureas with aliphatic or aromatic aldehydes and p-toluenesulfinic acid and gives access to a large number of tosyl substituted (thio)ureas **1** (R^2 = H, alkyl, aryl). It should be mentioned that the target amidoalkylation reagents **1** are obtained in very good yields and in high regio- and chemoselectivity. We showed that the compounds **2** easily react with hydrazoic acid in water at 20 °C to produce (azidomethyl)thioureas or (azidomethyl)ureas **3**.

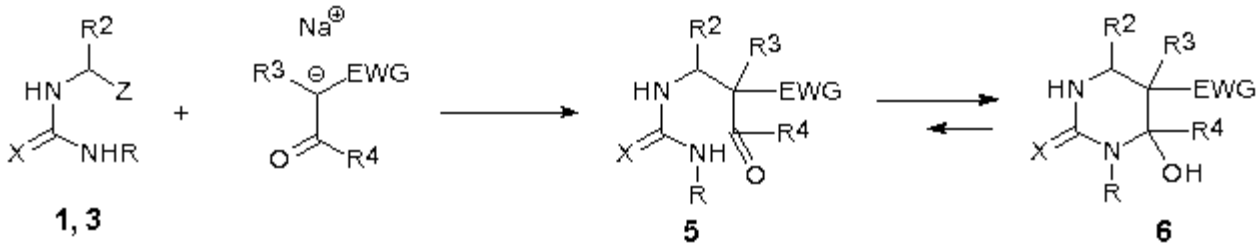
Scheme 2



X = S, O; R, R1 = H, Me, Ph; R2 = H, Me, Et, Pr, Ph, etc.

As second building block for the pyrimidine ring construction, in the present work we used various acyclic and cyclic carbonyl compounds **4** containing also electron-withdrawing groups at the a-position. We found that the tosyl or azido group of thioureas and ureas **1, 3** is readily replaced upon the reaction of these compounds with sodium enolates of **4** under mild conditions (acetonitrile or ethanol, 20 °C, 1-4 hours) to give the corresponding a-substituted products **5** which spontaneously undergo heterocyclization into 5-functionalized 4-hydroxyhexahydropyrimidine-2-thiones/ones **6** in good yields (Scheme 3). The amidoalkylation and cyclization proceed in high diastereoselectivity.

Scheme 3

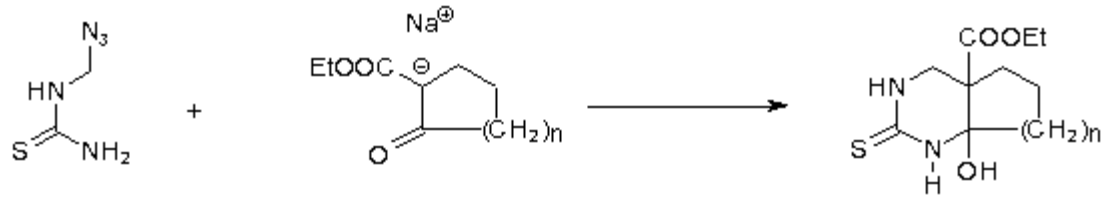


1, 3 **5** **6**

Z = Ts (1), N_3 (3); X = S, O; R^2, R^4 = H, alkyl, aryl; R^3 = H, alkyl, benzyl.
EWG = electron-withdrawing group, such as COOR, C(O)R, SO_2R, etc.

The described methodology is very general and can be used for the synthesis of a wide variety of pyrimidine-2-thiones/ones including condensed heterocyclic systems. For example, the perhydrocyclopenta[d]pyrimidine-2-thione **7** and perhydroquinazoline-2-thione **8** were obtained as single diastereomers by the reaction of (azidomethyl)thiourea with ethyl 2-oxocyclopentanecarboxylate or ethyl 2-oxocyclohexanecarboxylate (acetonitrile, 20 °C, 5-6 hours) in 73 and 69 % yields correspondingly (Scheme 4).

Scheme 4

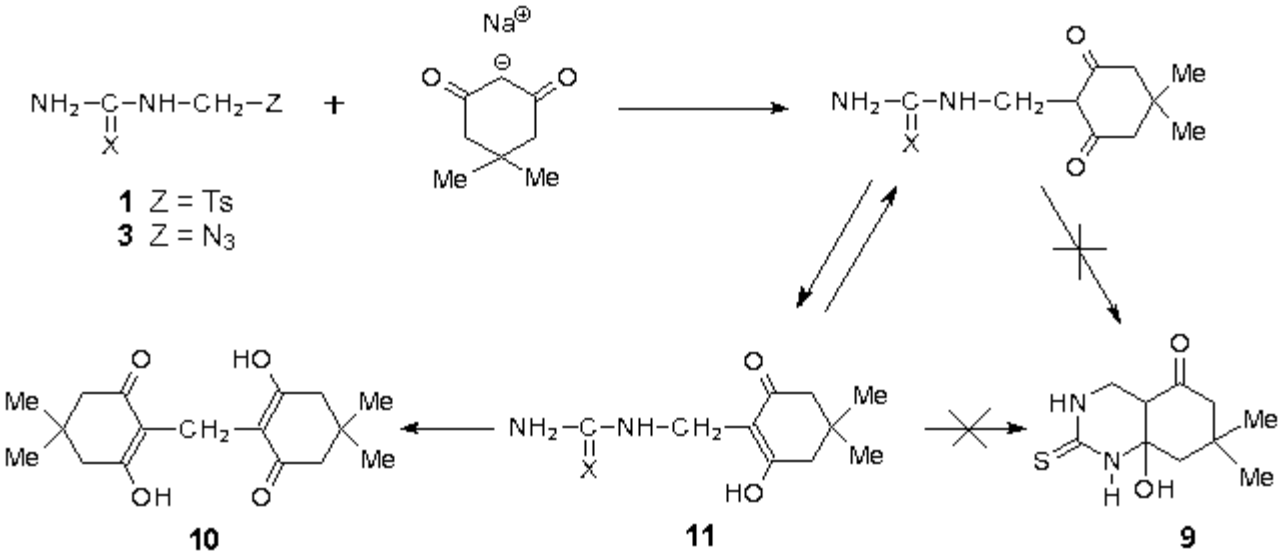


3

7 n = 1
8 n = 2

It is interesting to note that among investigated reactions only the reaction of (tosylmethyl)thiourea or (azidomethyl)thiourea with the sodium enolate of dimedone failed to give the desirable pyrimidine-2-thione **9**. Instead of **9** we obtained methylene-bis-dimedone **10** in 47 % yield (Scheme 5). Such course of the reaction can be explained by instability of the intermediate **11** under the reaction conditions.

Scheme 5



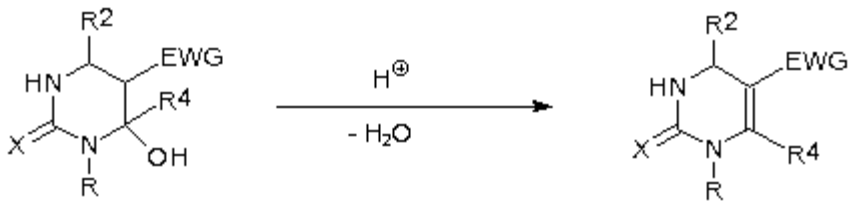
1 Z = Ts
3 Z = N_3

10 **11** **9**

Elimination of water from the hexahydropyrimidine-2-thiones/ones **6** (R^3 = H) leads to the formation of 5-

functionalized 1,2,3,4-tetrahydropyrimidene-2-thiones/ones **12** (Biginelli compounds) in excellent yields. These compounds are also obtained directly from the tosyl or azido substituted (thio)ureas **1, 3** without isolation of the intermediate 4-hydroxyhexahydropyrimidine-2-thiones/ones **6** in good overall yields (Scheme 6).

Scheme 6



6 **12**

X = S, O; R^2, R^4 = H, alkyl, aryl; EWG = COOR, C(O)R, SO_2R, etc.

Experimental Part

Below we presented some general procedures for the pyrimidine synthesis.

4-Hydroxyhexahydropyrimidine-2-thiones **6**: To a stirred suspension of NaH (2.73 mmol) in 5 ml of dry acetonitrile was added a solution of C-H acid **4** (2.73 mmol) in 5 ml of acetonitrile dropwise over a period of 5 min. Then, thiourea **1** or **3** (2.26 mmol) was added all at once and the reaction mixture was stirred at r.t. for a few hours, concentrated in vacuo. The residue was treated with water (4 ml), the precipitate formed on cooling was collected by filtration, washed with cold water and dried to afford **6**.

1,2,3,4-Tetrahydropyrimidine-2-thiones **12***:* A solution of **6** (0.42 mmol) and $TsOH \cdot H_2O$ (0.008 g) in 2 ml of anhydrous ethyl alcohol was refluxed for a hour. Then, the reaction mixture was cooled to -5 °C, precipitate formed was collected by filtration, washed with cold ethyl alcohol, dried to yield **12**.

Conclusion

Thus, the methodology based on the preparation of a-tosyl and a-azido substituted thioureas and ureas followed by the reaction with sodium enolates of carbonyl compounds provides a simple powerful tool for the synthesis of a large number of hydrogenated multifunctional pyrimidine-2-thiones/ones. Mild reactions conditions, good yields, availability of all the starting compounds, flexibility, stereoselectivity, great synthetic potential make the described method very promising. This methodology can be easily extended to the synthesis of others nitrogen containing heterocycles.

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