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[A0016]

NEW SYNTHETIC APPLICATIONS OF a-UREIDOALKYLATION IN HETEROCYCLIC CHEMISTRY

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Abstract: Some general methods for carbon-heteroatom, carbon-hydrogen and carbon-carbon bond formation at the 4 position of hexahydropyrimidine-2-thiones/ones based on the usage of ureidoalkylation have been developed.

Keywords: Hexahydropyrimidine-2-thiones/ones, 1,2,3,4-tetrahydropyrimidine-2-thiones/ones, imidazolidine-2-ones, imidazoline-2-ones, ureidoalkylation

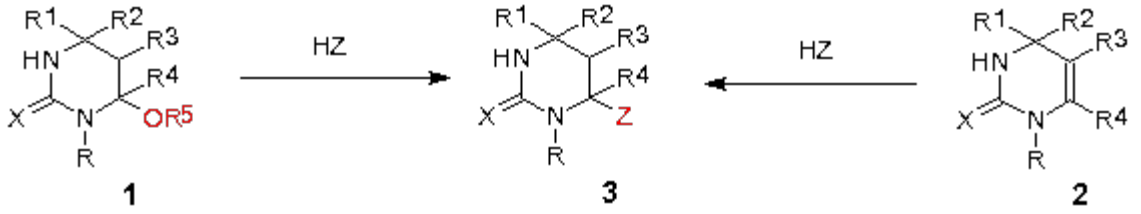
Introduction

Reactions of a,b-unsaturated aldehydes and ketones with thioureas and ureas [1], b-isothiocyanatocarbonyl compounds with amines [2] and b-aminocarbonyl compounds with isothiocyanates [3] are convenient methods for the synthesis of hydrogenated pyrimidine ring. The 4-hydroxyhexahydropyrimidine-2-thiones/ones, 4-alkoxyhexahydropyrimidine-2-thiones/ones and 1,2,3,4-tetrahydropyrimidine-2-thiones/ones obtained as the result of these reactions are multifunctional compounds with several interrelated reaction centers and this also determines the abundant synthetic possibilities of these compounds in preparation of various heterocycles [1-4]. One of the most specific reactions of the compounds indicated is the reaction with nucleophiles at the 4 position - the ureidoalkylation reaction. While amidoalkylation is widely used in organic synthesis [5], synthetic applications of ureidoalkylation, especially in heterocyclic chemistry, are quite limited [6]. In the course of our studies on hydrogenated nitrogen containing heterocycles with potential biological activity we have developed some general methods for carbon-heteroatom, carbon-hydrogen and carbon-carbon bond formation at the 4 position of hexahydropyrimidine-2-thiones/ones and related compounds. Here we present some results of our investigation.

Results and Discussion

We found that 4-hydroxy- and 4-alkoxyhexahydropyrimidine-2-thiones/ones **1** and 1,2,3,4-tetrahydropyrimidine-2-thiones/ones **2** react with a wide variety of O-nucleophiles (water, alcohols), S-nucleophiles (hydrogen sulfide, alkanethiols, arylsulfinic acids, dithiocarbamic acid, xanthic acid, etc.), N-nucleophiles (ammonia, primary alkylamines and arylamines, hydroxylamine, hydrazine and arylhydrazines, thiosemicarbazide, urea, thiourea, thiocyanic acid, hydrazoic acid, etc.), H-nucleophiles (sodium tetrahydroborate - trifluroacetic acid), C-nucleophiles (secondary and tertiary arylamines) to form the 4-substituted hexahydropyrimidine-2-thiones/ones **3** in yields good to excellent (Scheme 1).

Scheme 1

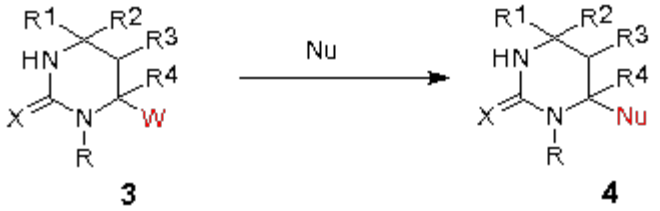


X = S, O; R^5 = H, alkyl.
HZ = H_2O, ROH, H_2S, RSH, ArSOOH, EtOC(S)SH, $NH_2C(S)SH$, NH_3, RNH_2, $ArNH_2$, NH_2OH, NH_2NH_2, $ArNHNH_2$, $NH_2C(S)NHNH_2$, $NH_2C(O)NH_2$, $NH_2C(S)NH_2$, HNCS, HN_3, $NaBH_4$ - CF_3COOH, ArNHR, $ArNR_2$, etc.

We studied influence of structure of reagents, type and concentration of catalyst, solvent, reaction conditions upon yields of ureidoalkylation products, chemo- and stereoselectivity of reactions. We showed that as a rule the investigated reactions are catalysed by acids. It is interesting to note that reactions of pyrimidines **1**, **2** (R = H) with such nucleophiles as alcohols, alkanethiols, alkyl- and arylamines occur also in the presence of strong bases. In the case of some N-nucleophiles (hydroxylamine, hydrazines, etc.) the reactions proceed without addition of catalyst. We found that the diastereoselectivity of ureidoalkylation in the most of cases is very high. As illustration, in the table 1 we presented selected data on the reactions of trans-4-hydroxy-6-methylhexahydropyrimidine-2-thione 1 (R = R^2 = R^3 = R^4 =R^5 = H, R^1 = Me) with some nucleophiles.

Thus, the direct reactions of the pyrimidines **1**, **2** with various nucleophiles give access to a large number of substituted hexahydropyrimidine-2-thiones **3**. However, our efforts to obtain the desired products by the reactions of the compound **1**, **2** with some types of nucleophiles mainly C-nucleophiles failed. It can be explained by rather poor ureidoalkylation properties of these heterocycles. We found that some of the obtained compounds **3** namely bearing azido, arylsulfonyl, (ethoxythiocarbonyl)thio, isothiocyanato and acetoxy groups at the 4 position are very efficient ureidoalkylation reagents. They react easily not only with a wide variety of O-, S-, N- and H-nucleophiles but also with C-nucleophiles (enolates, Grignard reagents, cyanide anion) under very mild conditions to afford the corresponding 4-substituted products **4** (Scheme 2) in good yields. These reagents are especially useful in ureidoalkylation of labile (in reaction conditions) nucleophiles (for example, sugars) as well as in the cases when the starting pyrimidines **1**, **2** are inefficient.

Scheme 2

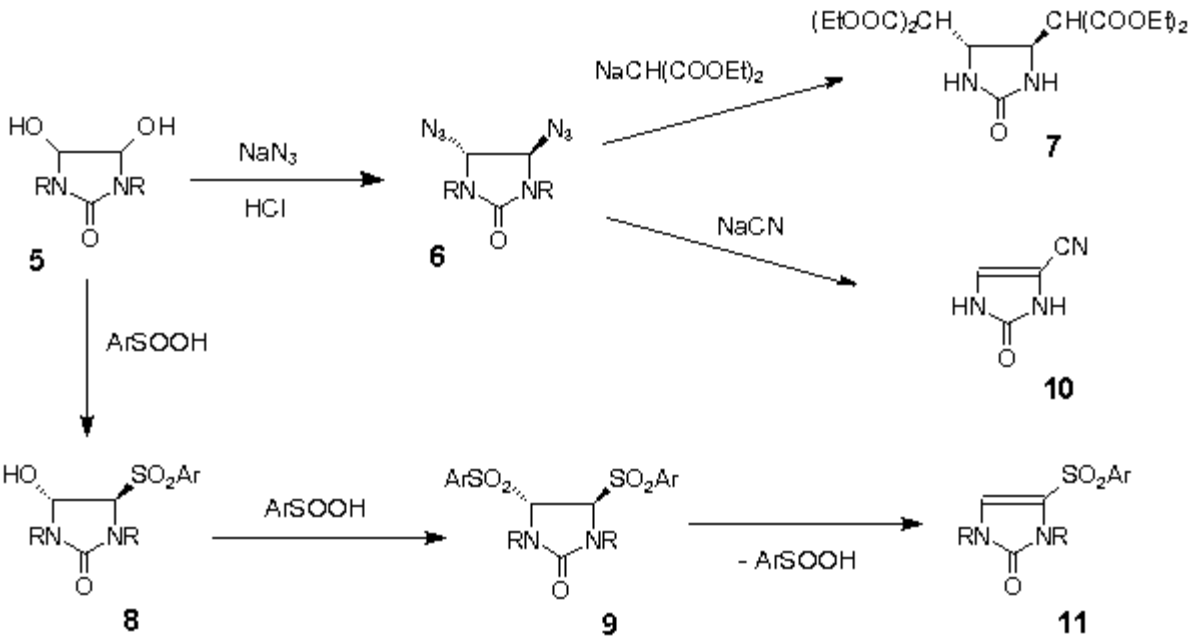


X = S, O. W = N_3, SO_2Ar, SC(S)OEt, NCS, OAc. Nu = nucleophile.

We showed that these reactions proceed usually with good diastereoselectivity which depends on the structure of reagents and solvent. In the table 2 some of the obtained results for the reactions of 4-substituted 6-methylhexahydropyrimidine-2-thiones **3** with some nucleophiles at 20 °C are demonstrated .

The above approach can be easily extended for the synthesis of various heterocycles related to hexahydropyrimidine-2-thiones/ones. For example, starting from readily available 4,5-dihydroxyimidazolidine-2-ones **5** we obtained the 4,5-disubstituted imidazolidine-2-ones **6**-**9** and 4-substituted imidazoline-2-ones **10**, **11** as shown in Scheme 3.

Scheme 3



R = H, Me. Ar = Ph, 4-MeC$_6$H$_4$.

Conclusion

Thus, we have shown that the readily available 4-hydroxy(or alkoxy)hexahydropyrimidine-2-thiones/ones and 1,2,3,4-tetrahydropyrimidine-2-thiones/ones can serve as the starting compounds in the synthesis of a large variety of substituted hexahydropyrimidine-2-thiones/ones via ureidoalkylation. The synthesis includes either the direct reactions of the starting heterocycles with nucleophiles or the transformations of these heterocycles into the 4-azido(or arylsulfonyl, ethoxythiocarbonylthio, isothiocyanato, acetoxy)hexahydropyrimidine-2-thiones/ones followed by the reactions with suitable nucleophiles.

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Comments

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