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Synthesis and Reactivity of 5-Functionalized 4-Hydroxyhexahydropyrimidine-2-thiones/ones

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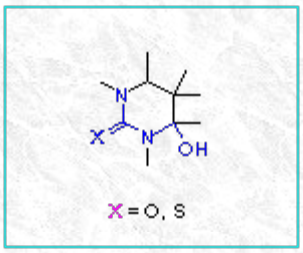
Abstract: A new general two-steps synthesis of 5-functionalized 4-hydroxyhexahydropyrimidine-2-thiones/ones has been developed. This synthesis are based on preparation of the a-azido and a-tosyl(thio)ureas **2**, **5** followed by reaction with enolates of a-functionally substituted ketones. All the obtained hydroxypyrimidines **8a-c** are readily converted into the corresponding 5-functionalized 1,2,3,4-tetrahydrohydropyrimidine-2-thiones/ones 9**a-c** by heating in the presence of acids. Treatment of the 4-acylsubstituted 4-hydroxyhexahydropyrimidine-2-thiones/ones **8b** with bases in acetonitrile gives the N-acyl-N'-(b-oxoalkyl)thioureas/ureas **10** in result of rearrangement including C(4)-C(5)-bond cleavage in **8b**. Reaction of the (thio)ureides **10** and the 5-acylsubstituted 4-hydroxyhexahydropyrimidine-2-thiones/ones **8b** with KOH in water leads to the 4-hydroxyhexahydropyrimidine-2-thiones/ones **11** without the acyl group at the C(5) position. Treatment of the ethyl 4-hydroxy-2-thioxohexahydropyrimidine-5-carboxylates **8a** with bases in acetonitrile depending on the starting compounds structure yields either the 5,6-dihydro-2-thiouracils **12**, **13** or the products of C(4)-C(5)-bond cleavage **14**.

Keywords: N-(azidomethyl)thiourea, N-(1-tosyl-1-alkyl)thioureas/ureas, 4-hydroxyhexahydropyrimidine-2-thiones/ones, 1,2,3,4-tetrahydropyrimidine-2-thiones/ones, N-acyl-N'-(b-oxoalkyl)thioureas/ureas, 5,6-dihydro-2-thiouracils.

Introduction



4-Hydroxyhexahydropyrimidine-2-thiones/ones are of great interest due to their high synthetic potential. It can be explained by presence of the interconnected N,O-acetal and thiourea/urea moieties in their molecules as well as by ability of their conversion to the acyclic isomeric forms (ring-chain isomerism) [1]. Thus, it is not surprising that these compounds are versatile precursors in syntheses of a large variety of heterocycles. For example, they were used in syntheses of fully and partly hydrogenated pyrimidines [2], 1,3-thiazines [3], pyridines [4], condensed heterocycles [5], etc. Besides, 4-hydroxyhexahydropyrimidine-2-thiones/ones manifest various useful properties. Some of these compounds possess herbicidal [6] and radioprotective [7] activities, improve quality of textiles [8], etc.

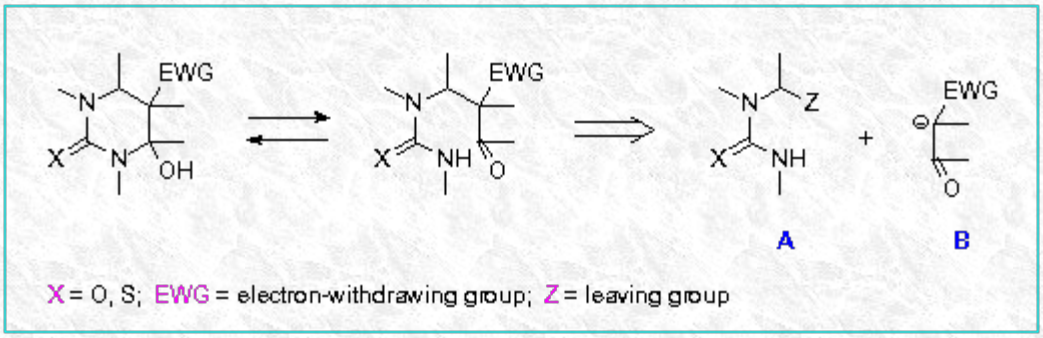
At present time there are three main methods for the synthesis of 4-hydroxyhexahydropyrimidine-2-thiones/ones from acyclic precursors:

- reaction of b-isothiocyanato carbonyl compounds with ammonia or primary amines [9];
- reaction of b-amino aldehydes or ketones with alkyl or aryliso(thio)cyanates [10];
- reaction of a,b-unsaturated aldehydes or ketones with (thio)ureas [11].

It should be noted that according to these procedures it is difficult or impossible to obtain 4-hydroxyhexahydropyrimidine-2-thiones/ones bearing a functional group at the C(5) position of pyrimidine ring. That is why 5-functionalized analogs of 4-hydroxyhexahydropyrimidine-2-thiones/ones are scarcely known, and their chemistry and biological properties remain unexplored. We report here on a novel, general method for convenient preparation of these heterocycles via ureidoalkylation and describe some their transformations.

Results and Discussion

In our retrosynthetic analysis of 5-functionalized 4-hydroxyhexahydropyrimidine-2-thiones/ones we considered the reaction of a-substituted (thio)ureas (**A**) with enolates of carbonyl compounds (**B**).

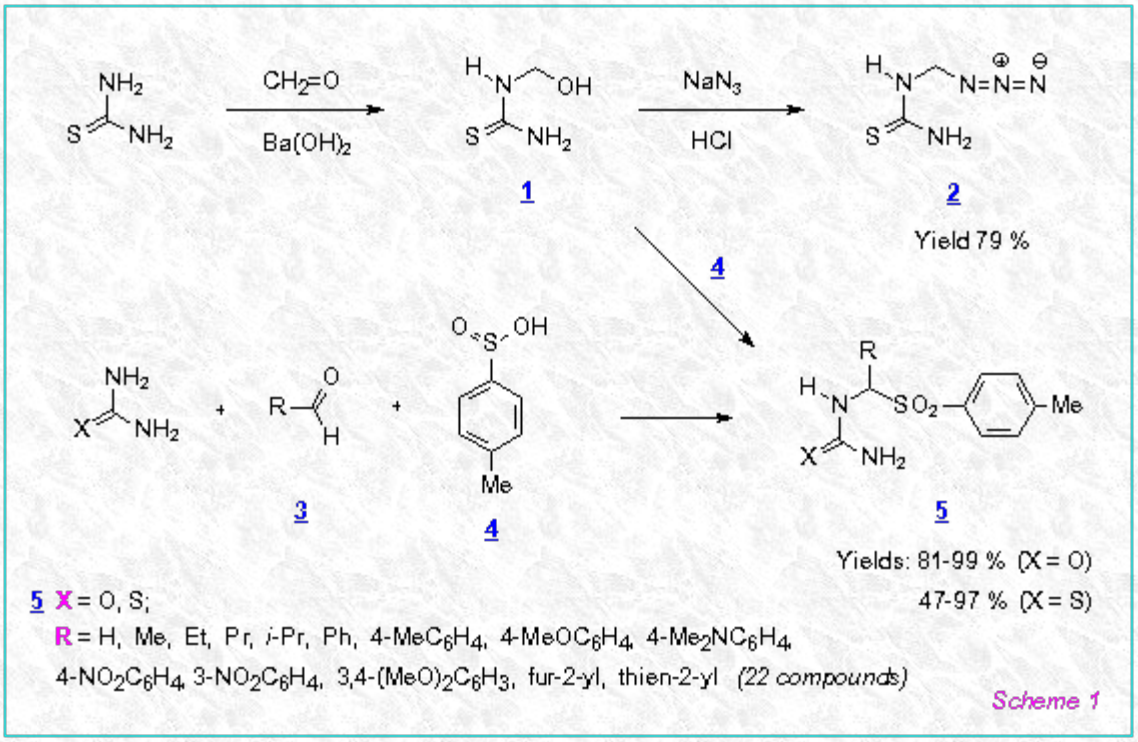


Effectiveness of the target pyrimidines synthesis depends on proper choice of leaving group **Z** in ureidoalkylation reagent (**A**). Recently we have demonstrated [12] that readily available cyclic (thio)ureas bearing azido or arylsulfonyl groups at the a-position to nitrogen are efficient in ureidoalkylation. We proposed that (thio)ureas **A** possessing the same leaving groups could serve as key intermediates in the synthesis of 4-hydroxyhexahydropyrimidine-2-thiones/ones.

Synthesis of a-azido or a-tosyl substituted thioureas and ureas

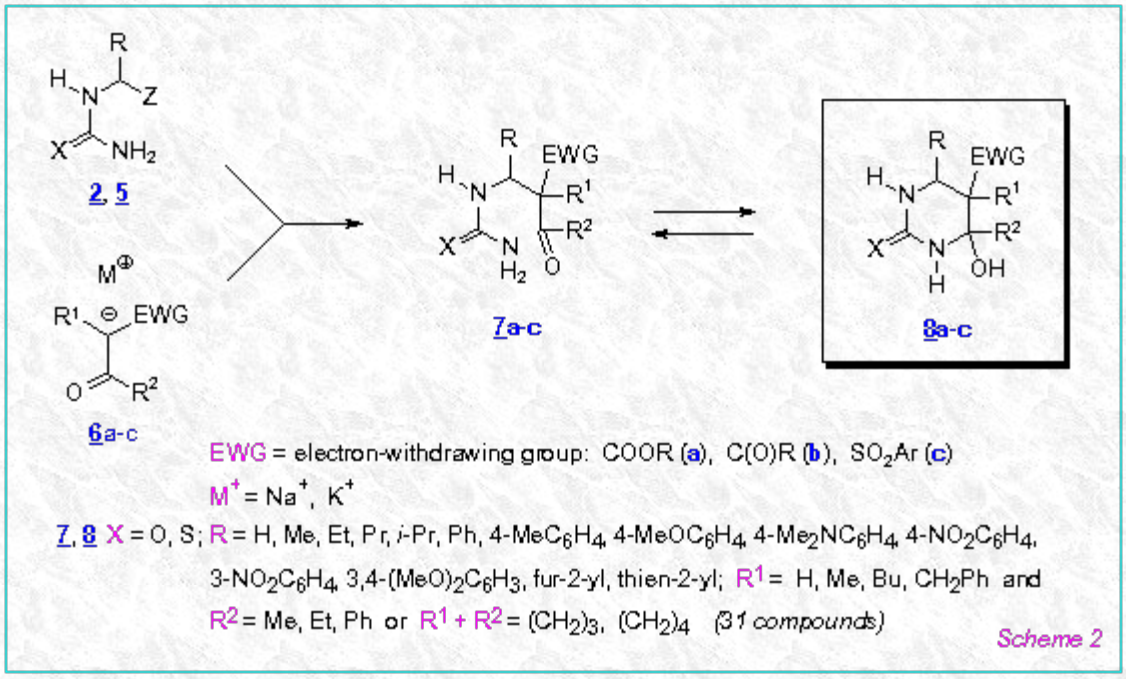
a-Azido or a-tosyl substituted (thio)ureas **2**, **5** served as the starting compounds for the pyrimidine synthesis. They

were readily obtained in 1-2 steps from thiourea or urea in good yields. Thus, N-(azidomethyl)thiourea **2** and N-(tosylmethyl)thiourea **5** (R = H) were prepared by the reaction of methylolthiourea **1** with hydrazoic acid or *p*-toluenesulfinic acid in water (*Scheme 1*). a-Substituted tosyl(thio)ureas **5** were synthesized by the treatment of thiourea or urea with aliphatic or aromatic aldehydes and *p*-toluenesulfinic acid in water. The obtained (thio)ureas **2**, **5** owing to their good purity were used for the pyrimidine synthesis without further purification.



Synthesis of 5-functionalized 4-hydroxyhexahydropyrimidine-2-thiones/ones

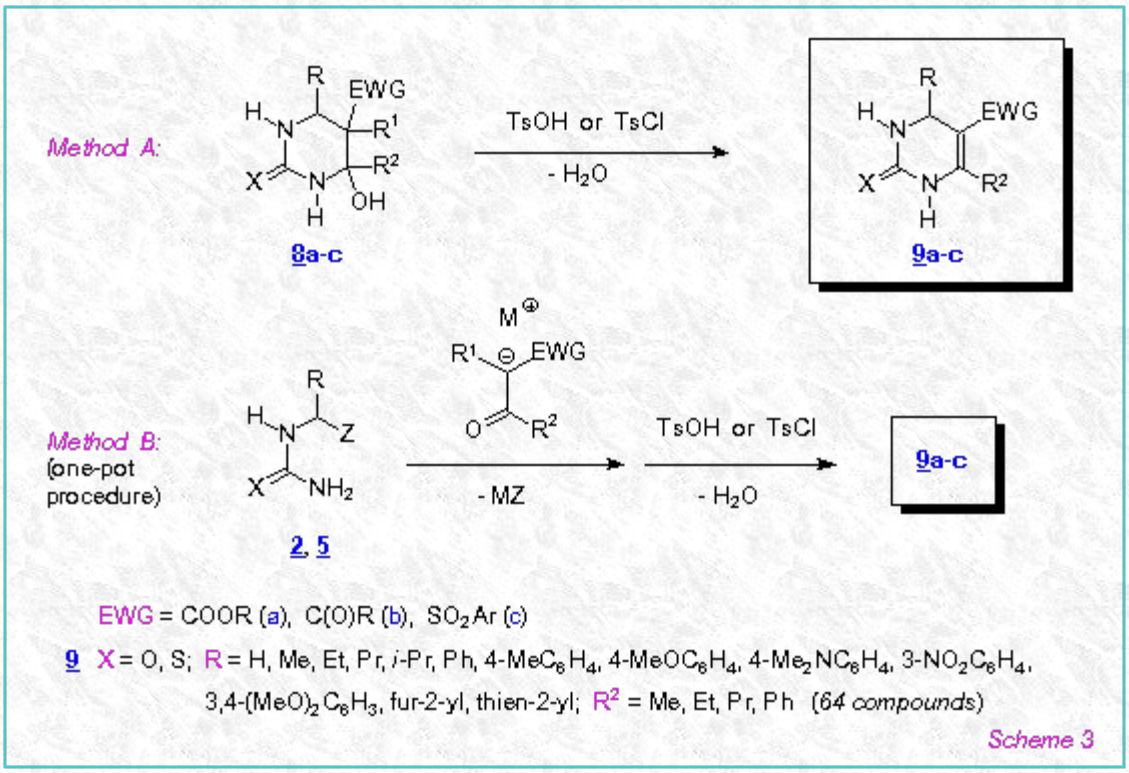
We found that the (thio)ureas **2**, **5** reacted redily (r.t., 2-6 h) with enolates of various b-oxoesters, 1,3-dicarbonyl compounds or a-arylsylfonylketones **6a-c** generated *in situ* by treatment of the corresponding CH-acids with KOH in ethanol or with NaH in acetonitrile to give the corresponding 5-functionalized 4-hydroxyhexahydropyrimidine-2-thiones/ones **8a-c** in a regioselective manner (*Scheme 2*). The products were formed in high diastereomeric purity (*de* 52-100 %).



Scheme 2

Synthesis of 5-functionalized 1,2,3,4-tetrahydropyrimidine-2-thiones/ones

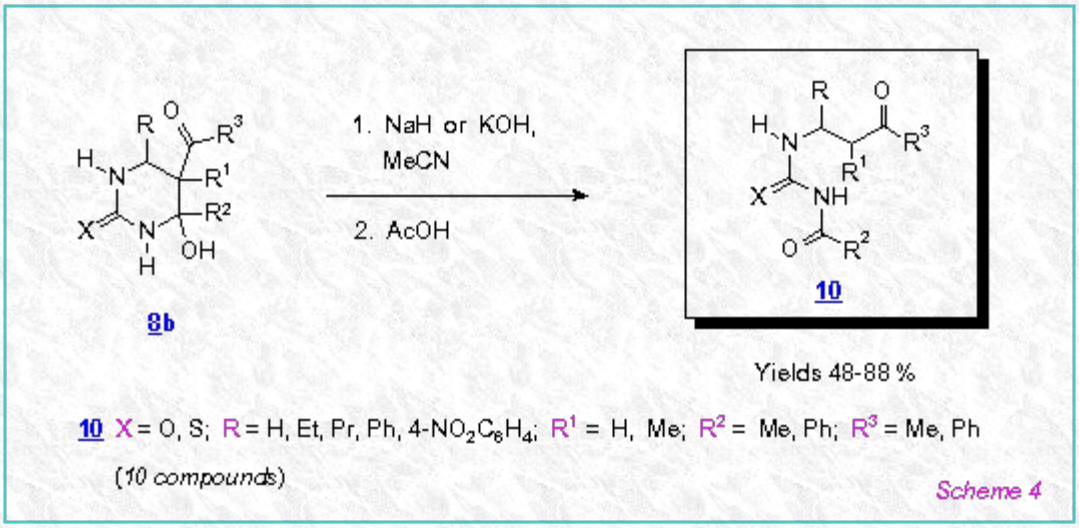
We investigated behaviour of the compounds **8a-c** towards acids and bases. We found that these compounds were readily dehydrated by refluxing in ethanol or acetonitrile in the presence of TsOH or TsCl (*method A*) to afford 5-functionalized 1,2,3,4-tetrahydropyrimidine-2-thiones **9a-c** in excellent yields (Scheme 3). The compounds **9a-c** were also prepared in good overall yields according to *one-pot* procedure by reaction of the (thio)ureas **2**, **5** with the enolates **6a-c** followed by acidification and refluxing of the reaction mixtures (*method B*).



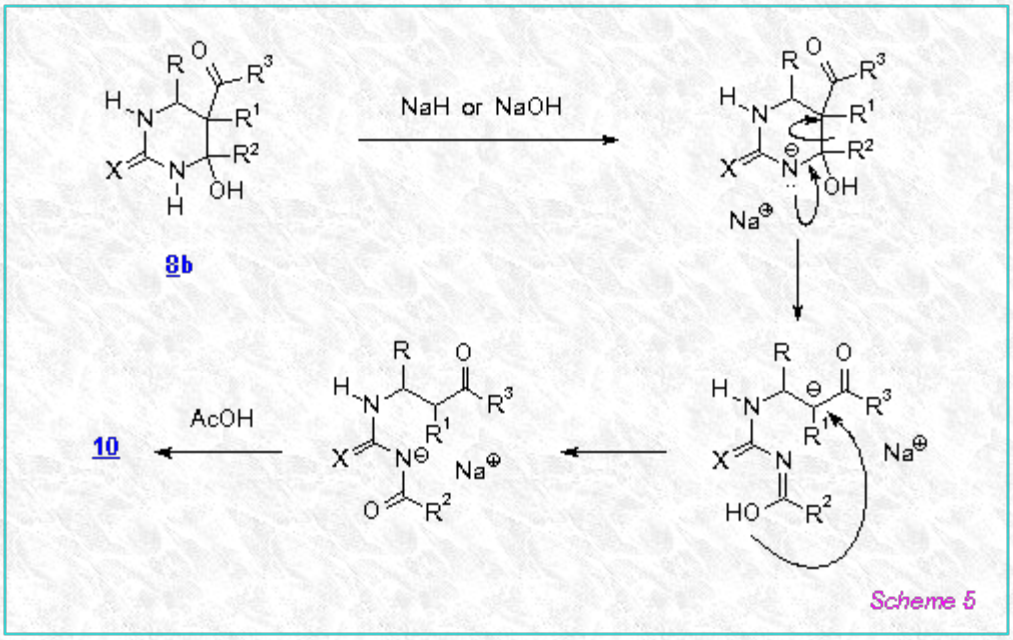
Scheme 3

Rearrangement of 5-acyl-4-hydroxyhexahydropyrimidine-2-thiones/ones in the presence of bases

We demonstrated that 5-acyl-4-hydroxyhexahydropyrimidine-2-thiones/ones **8b** underwent rearrangement in the presence of NaH or NaOH in acetonitrile to produce, after acidification of the reaction mixtures, unknown N-acyl-N'-(b-oxoalkyl)thioureas and ureas **10** (*Scheme 4*).

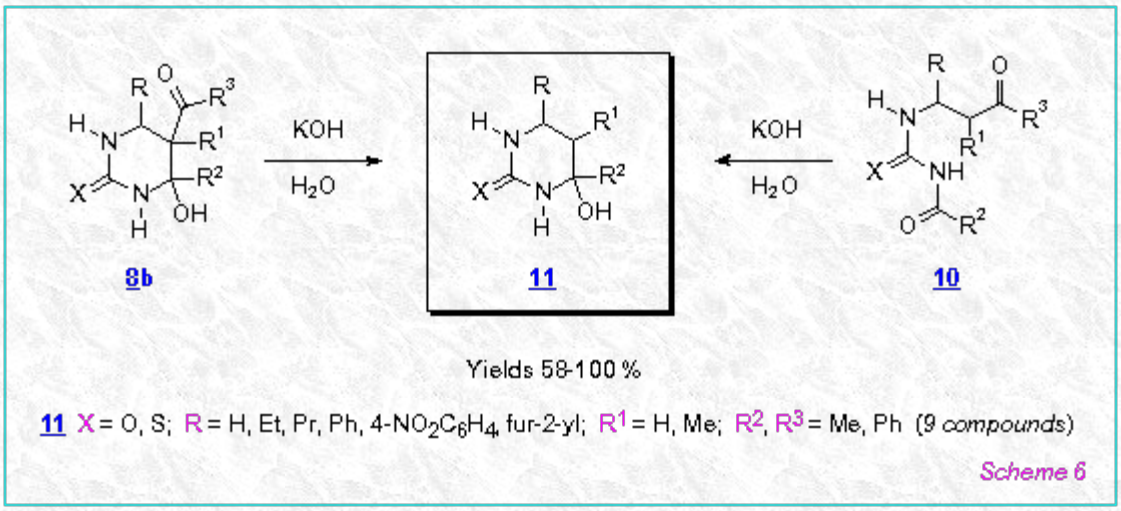


Proposed mechanism of this unusual rearrangement is presented on *Scheme 5* and includes C(4)-C(5)-bond cleavage in the anion of **8b**.



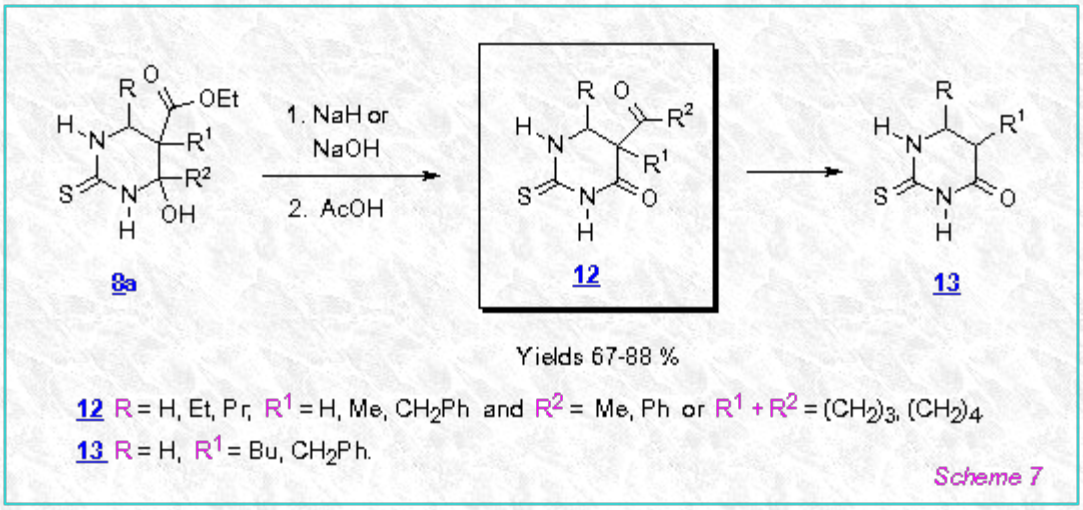
Synthesis of 4-hydroxyhexahydropyrimidine-2-thiones/ones

The obtained (thio)ureides **10** were easily hydrolized by treatment of KOH in water to give the 4-hydroxypyrimidines **11** (*Scheme 6*). The latter were also produced directly starting from the 5-acyl-4-hydroxypyrimidines **8b** (KOH, water). Probably, this transformation proceeds *via* the retro-Claisen reaction in the acyclic isomeric form of **8b**.

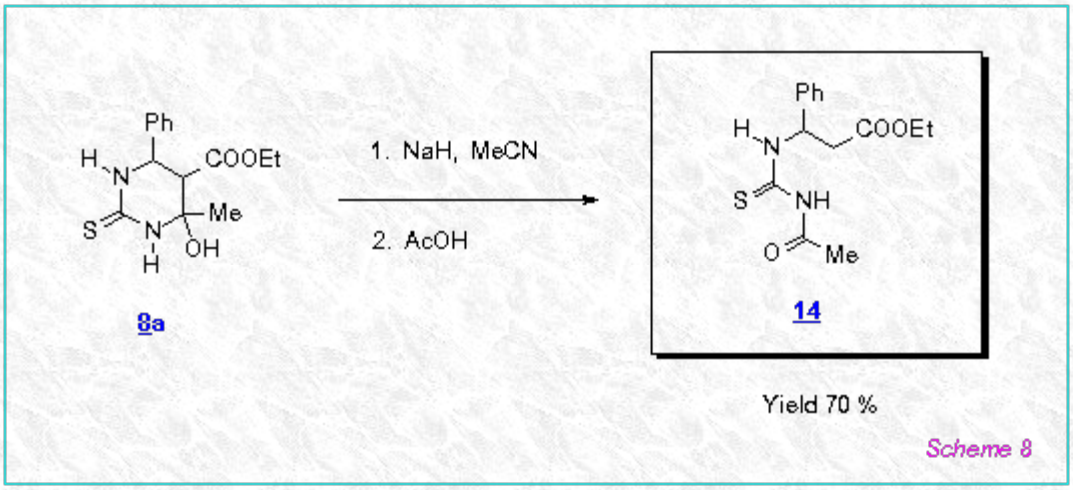


Transformations of ethyl 4-hydroxy-2-thioxohexahydropyrimidine-5-carboxylates in the presence of bases

Reaction of ethers of 4-hydroxy-2-thioxohexahydropyrimidine-5-carboxylic acids **8a** with bases (NaH or NaOH in acetonitrile) is more complex than for **8b**. In the case of 6-unsubstituted or 6-alkyl substituted **8a**, their transformation into 5-acyl-5,6-dihydro-2-thiouracils **12** took place (*Scheme 7*). Apparently, this reaction proceeds *via* the acyclic isomeric form of **8a**. Sometimes the deacylation products of **12** namely 5,6-dihydro-2-thiouracils **13** were formed.



In the case of 6-phenyl substituted **8a**, its rearrangement into the thioureide **14** occured (*Scheme 8*). Probably, mechanism of this rearrangement is the same as for the synthesis of **10**.



Conclusion

Thus, the present work demonstrates that 5-functionalized 4-hydroxyhexahydropyrimidine-2-thiones/ones can be prepared by reaction of readily available a-tosyl or a-azido substituted (thio)ureas with enolates of a-substututed ketones (C-N-C-N + C-C ring construction). The obtained hydroxypyrimidine can serve as starting compounds in syntheses of a large number of multifunctional pyrimidine-2-thiones/ones. Mild reaction conditions, good overall yields, high flexibility make the described methods of pyrimidine syntheses very promising.

References

1. Unkovskii, B.V.; Ignatova, L.A.; Zaitseva, M.G. *Khim. Geterotsikl. Soedin.* (Rus), **1969**, 889; Unkovskii, B.V.; Ignatova, L.A.; Zaitseva, M.G.; Donskaya M.M. *ibid*, **1965**, 586.

2. Shutalev, A.D.; Alekseeva, S.G. *Khim. Geterotsikl. Soedin.* (Rus), **1995**, 377; Shutalev, A.D.; Komarova, E.N.; Pagaev, M.T.; Ignatova, L.A. *ibid*, **1993**, 1259; Zigeuner, G.; Galatik, W.; Lintshinger, W.-B.; Wede, F. *Monatsh. Chem.*, **1975**, *106*, 1219; Ovechkina, G.I.; Ignatova, L.A.; Ratomskaya, M.G.; Unkovskii, B.V. *Khim. Geterotsikl. Soedin.* (Rus), **1971**, 1258; Zigeuner, G.; Rauter, W. *Monatsh. Chem.*, **1965**, *96*, 1950.

3. Unkovskii, B.V.; Ignatova, L.A. *Khim. Geterotsikl. Soedin. (Rus)*, **1969**, 896.

4. Zigeuner, G.; Lintschinger, W.-B.; Fuchsgruber, A.; Kollmann, K. *Monatsh. Chem.*, **1976**, *107*, 155.

5. Singh, H.; Kumar, S. *Tetrahedron*, **1987**, *43*, 2177; Zigeuner, G.; Kollmann, K.; Lintschinger, W.-B.; Fuchsgruber, A. *Monatsh. Chem.*, **1976**, *107*, 183.

6. Krenzer, J. *US Pat. 3951976* (**1976**), Cl C 07D 239/00.

7. Rolevitch, I.V.; Ignatova, L.A.; Shutalev, A.D. *Unpublished data*.

8. Petersen, H.; Pai, P.; Reichert, M. *Eur. Pat. Appl. 33115* (**1981**), Cl D 06M 15/54.

9. Ignatova, L.A.; Shutalev, A.D.; Shingareeva, A.G.; Dymova, S.F.; Unkovskii, B.V. *Khim. Geterotsikl. Soedin.* (Rus), **1985**, 260; Mathes, R.A. *J. Amer. Chem. Soc.*, **1953**, *75*, 1747.

10. Shutalev, A.D.; Ignatova, L.A.; Unkovskii, B.V. *Khim. Geterotsikl. Soedin.* (Rus), **1984**, 548; Ovechkin, P.L.; Ignatova, L.A.; Unkovskii, B.V. *ibid*, **1972**, 941.

11. Zimmermann, R.; Brahler, B.; Hotze, H. *Pat. 1065849 BRD* (**1961**); Zimmermann, R.; Brahler, B.; Hotze, H. *Angew. Chem.*, **1960**, *72*, 78.

12. Shutalev, A.D. *Khim. Geterotsikl. Soedin.* (Rus), **1993**, 1645; Shutalev, A.D. *ibid*, **1993**, 1389; Shutalev, A.D.; Ignatova, L.A. *ibid*, **1991**, 228; Shutalev, A.D.; Ignatova, L.A.; Unkovskii, B.V. *ibid*, **1990**, 133.

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