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A New Route for the Synthesis of Cyclic Thioureas and Related Compounds

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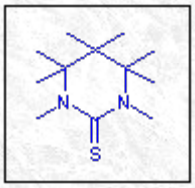
Abstract: Six-membered cyclic thioureas can be prepared by a convenient stereoselective method based on the reduction of readily available 4-hydroxy(or 4-alkoxy)hexahydropyrimidine-2-thiones or 1,2,3,4-tetrahydropyrimidine-2-thiones with $NaBH_4$ - CF_3COOH. Alternative method of the preparation of the target compounds includes reaction of 4-azido-, 4-acetoxy- or 4-arylsulfonylhexahydropyrimidine-2-thiones with $NaBH_4$.

Keywords: hexahydropyrimidine-2-thiones/ones, 1,2,3,4-tetrahydropyrimidine-2-thiones, tetrahydro-1,3-thiazine-2-thiones, sodium tetrahydroborate - trifluoacetic acid

Introduction



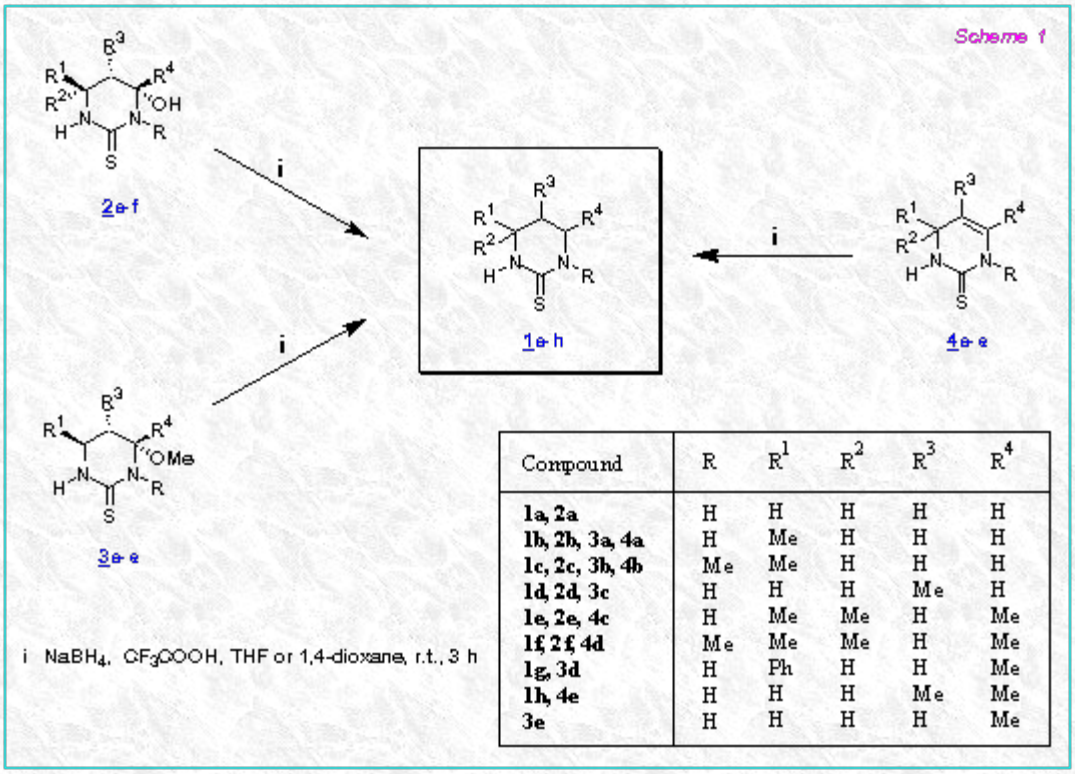
Six-membered cyclic thioureas, namely hexahydropyrimidine-2-thiones **1**, are currently of interest due to their biological activity and other useful properties [1]. The application of the substances in organic synthesis has been described [2]. Besides, these compounds are valuable objects for spectroscopic and theoretical investigations.

The general method for synthesis of hexahydropyrimidine-2-thiones includes condensation of (N-C-C-C-N + C)- type. For example, they are prepared by cyclization of 1,3-diamines with thiophosgene, carbon disulfide, etc. [1]. However, this method suffers from the fact that rather often the starting 1,3-alkanediamines can not be easily obtained, especially in a stereoselective manner. In contrast, various 4-hydroxyhexahydropyrimidine-2-thiones **2**, 4-alkoxyhexahydropyrimidine-2-thiones **3** and 1,2,3,4-tetrahydropyrimidine-2-thiones **4** are readily available [3]. It is known that these compounds react with nucleophiles to give the corresponding 4-substituted hexahydropyrimidine-2-thiones [4]. We proposed that the reaction of **2-4** and some other 4-substituted hexahydropyrimidine-2-thiones with H-nucleophiles could provide a simple general method for the synthesis of the target compounds. We report here on new

convenient procedures for the preparation of six-membered cyclic thioureas by reduction of 4-hydroxy(or 4-alkoxy)hexahydropyrimidine-2-thiones, 1,2,3,4-tetrahydropyrimidine-2-thiones or some 4-functionally substituted hexahydropyrimidine-2-thiones. As reducing reagents we used sodium tetrahydroborate or sodium tetrahydroborate in the presence of carboxylic acids. Earlier the latter reducing system was successfully applied for the transformation of a-hydroxyalkylamides into N-alkylamides [5].

Results and Discussion

We found that the 4-hydroxyhexahydropyrimidine-2-thiones **2a-f** are readily reduced by $NaBH_4$ in the presence of CF_3COOH [molar ratio of **2** : $NaBH_4$: CF_3COOH 1 : (3-4) : (20-30)] (THF or 1,4-dioxane, r.t., 3 h) to form the corresponding hexahydropyrimidine-2-thiones **1a-f** in 83-99 % isolated yields (*Scheme 1*).



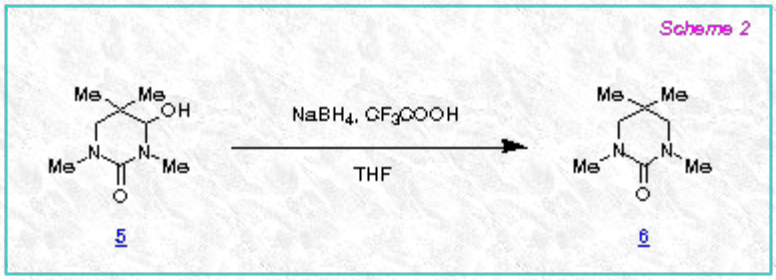
Compound	R	R^1	R^2	R^3	R^4
1a, 2a	H	H	H	H	H
1b, 2b, 3a, 4a	H	Me	H	H	H
1c, 2c, 3b, 4b	Me	Me	H	H	H
1d, 2d, 3c	H	H	H	Me	H
1e, 2e, 4c	H	Me	Me	H	Me
1f, 2f, 4d	Me	Me	Me	H	Me
1g, 3d	H	Ph	H	H	Me
1h, 4e	H	H	H	Me	Me
3e	H	H	H	H	Me

The reaction is usually carried out by the addition of CF_3COOH to the suspension of the pyrimidine and $NaBH_4$ in the solvent at 0 °C followed by stirring the reaction mixtures for 3 h at r.t. (*method A*). The reactions also proceed successfully with another order of the addition of the reagents: CF_3COOH and then dry pyrimidine are added to the suspension of $NaBH_4$ in the solvent cooled to 0 °C (*method B*) or $NaBH_4$ is added to the mixture of the pyrimidine, CF_3COOH and the solvent at 0 °C (*method C*).

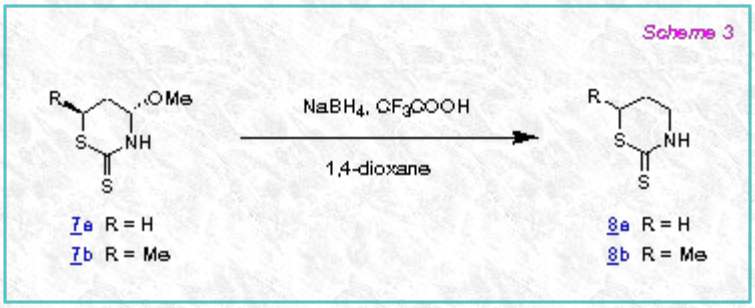
4-Alkoxyhexahydropyrimidine-2-thiones **3** and 1,2,3,4-tetrahydropyrimidine-2-thiones **4** can equally well serve as the starting material for the synthesis of hexahydropyrimidine-2-thiones. Thus the reaction of alkoxypyrimidines **3a-e** with $NaBH_4$ - CF_3COOH in the above mentioned conditions gives the compounds **1b-d,g** in 80-99.5 % yields. Similarly, the reduction of the tetrahydropyrimidines **4a-e** affords the compounds **1b,c,e,f,h** in 82-98 % yields. It should be mentioned that the reduction of both **3a** and **3e** results in the formation of the same pyrimidine **1b**.

The reduction of compounds **2-4** proceeds in a diastereoselective manner. For example, the reduction of the methoxypyrimidine **3d** possessing two chiral carbon atoms results in the formation of the compound **1g** which is a mixture of the *cis* and *trans* diastereoisomers (96:4 respectively). Analogously, achiral tetrahydropyrimidine **4e** is converted into the compound **1h** as a mixture of *cis* and *trans* isomers (24:76) where *trans* isomer is predominant.

The reduction with $NaBH_4$ - CF_3COOH is highly efficient as well for the synthesis of six-membered cyclic ureas, namely hexahydropyrimidine-2-ones, starting from the corresponding 4-hydroxy derivatives, as we showed by the conversion of the hydroxypyrimidinone **5** to the compound **6** in 95 % isolated yield (*Scheme 2*).

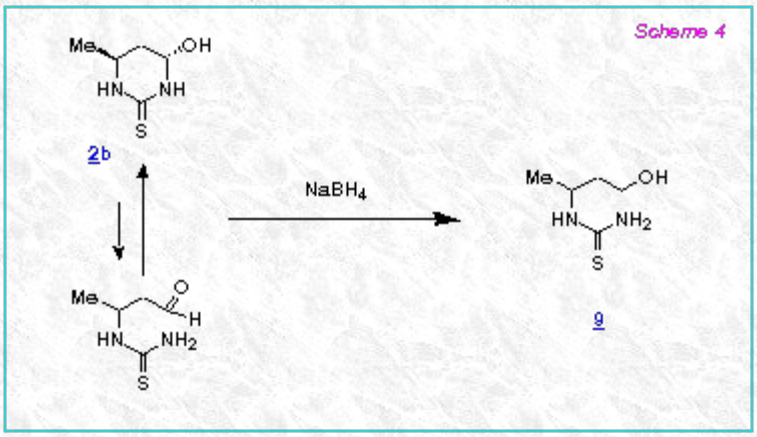


Evidently, $NaBH_4$ - CF_3COOH can be also applied for the reduction of other nitrogen containing heterocycles possessing amidoalkylation properties. For example, cyclic dithiocarbamates, namely the tetrahydro-1,3-thiazine-2-thiones **8a,b**, are obtained in 79 and 93 % yields respectively by the reduction of the 4-methoxytetrahydro-1,3-thiazine-2-thiones **7a,b** with $NaBH_4$ - CF_3COOH according to the *method A* (*Scheme 3*).



We found that the reductive ability of the $NaBH_4$ - RCOOH system decreases sharply when CF_3COOH is displaced by the weaker acetic acid. Actually, the reduction of the compounds **2b**, **4d** with $NaBH_4$ - CH_3COOH in THF does not practically occur.

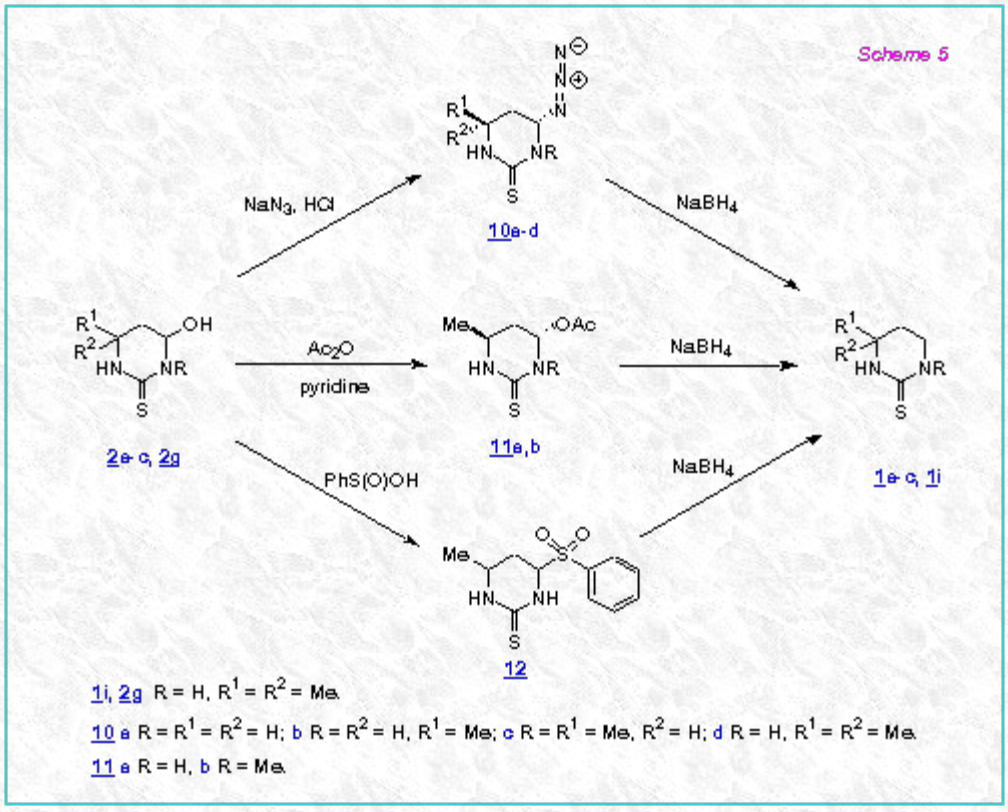
The reaction of 4-hydroxyhexahydropyrimidine-2-thiones with $NaBH_4$ proceeds differently without the addition of CF_3COOH. Thus, the reaction of the compounds **2b** with $NaBH_4$ (water, 50 ^oC) gives the product of the reduction of the aldehyde group of the acyclic isomeric form of **2b**, namely the N-(4-hydroxybut-2-yl)thiourea **9** (93% yield) (*Scheme 4*).



Thus, the first stage of the reactions studied is probably the generation of the acylimmonium cations from **2-4** in the presence of CF_3COOH. These cations are further subjected to nucleophilic attack at the C(4) position by the reducing agent, sodium tris(trifluoroacetoxy)hydroborate, formed by the reaction of $NaBH_4$ with CF_3COOH.

We proposed that it could be possible also to prepare six-membered cyclic thioureas by reduction of 4-substituted hexahydropyrimidine-2-thiones, bearing more easily leaving group at the C(4) position than hydroxy or alkoxy group, with $NaBH_4$ even in absence of CF_3COOH. Our preliminary investigations showed that 4-azido-, 4-acetoxy and 4-arylsulfonylhexahydropyrimidine-2-thiones can readily react with various nucleophiles under mild reaction conditions to produce the corresponding 4-substituted products [6]. Thus we studied reactions of the above mentioned compounds with $NaBH_4$.

We found that the 4-azidohexahydropyrimidine-2-thiones **10a-d** readily react with $NaBH_4$ in acetonitrile or DMFA at r.t. to afford the compounds **1a-c,i** in 89-100 % isolated yields. Reduction of 4-acetoxyhexahydropyrimidine-2-thiones **11a,b** and 4-phenylsulfonylhexahydropyrimidine-2-thione **12** with $NaBH_4$ in acetonitrile proceeds also easily and gives the compounds **1b,c** (*Scheme 5*).



The starting azidopyrimidines **10a-d** and phenylsulfonylpyrimidine **12** are obtained by reaction of the corresponding hydroxypyrimidines **2a-c,g** with hydrazoic acid or bensenesulfinic acid in water (r.t., 24 h) in yields more than 90 %. The acetoxypyrimidines **11a,b** are produced in 81-85 % yields by treatment of **2b,c** with Ac_2O in pyridine (r.t., 12 h).

Conclusion

Thus the present work shows that six-membered cyclic thioureas can be easily prepared according to two general procedures. The first route is stereoselective and includes direct reduction of readily available 4-hydroxy(or 4-alkoxy)hexahydropyrimidine-2-thiones and 1,2,3,4-tetrahydropyrimidine-2-thiones with $NaBH_4$ - CF_3COOH. The second procedure lies in synthesis of 4-azido-, 4-acetoxy- or 4-arylsulfonylhexahydropyrimidine-2-thiones followed

by their reduction with $NaBH_4$. Both the methods are very flexible. They give possibility to prepare not only a large number of cyclic thioureas but also related compounds, such as cyclic ureas, cyclic dithiocarbamates, etc.

References

1. Bogatskii, A.V.; Luk'yanenko, N.G.; Kirichenko, T.I. *Khim. Geterotsicl. Soedin.* (Rus), **1983**, 723 and references cited therein.

2. Sharma, S.D.; Arora, S.K.; Mehra, U. *Indian J. Chem.*, **1985**, *24*, 895; Chadha, V.K. *J. Indian Chem. Soc.*, **1977**, *54*, 878; Arya, V.P.; Shenoy, S.J. *Indian J. Chem.*, 1976, 14, 759; Chaudhary, H.S.; Pujari, H.K. *ibid*, **1972**, *10*, 766.

3. Ignatova, L.A.; Shutalev, A.D.; Shingareeva, A.G.; Dymova, S.F.; Unkovskii, B.V. *Khim. Geterotsikl. Soedin.* (Rus), **1985**, 260; Shutalev, A.D.; Ignatova, L.A.; Unkovskii, B.V. *ibid*, **1984**, 548; Zigeuner, G.; Galatik, W.; Lintschinger, W.-B.; Wede, F. *Monatsh. Chem.*, **1975**, *106*, 1219; Ovechkin, P.L.; Ignatova, L.A.; Unkovskii, B.V. *Khim. Geterotsikl. Soedin.*, **1972**, 941; Zigeuner, G.; Frank, A.; Dujmovits, H.; Adam, W. *Monatsh. Chem.*, **1970**, *101*, 1415; Unkovskii, B.V.; Ignatova, L.A.; Zaitseva, M.G. *Khim. Geterotsikl. Soedin.* (Rus), **1969**, 889; Zimmermann, R.; Brahler, B.; Hotze, H. *Pat. 1065849 BRD* (**1961**).

4. Shutalev, A.D.; Alekseeva, S.G. *Khim. Geterotsikl. Soedin.* (Rus), **1995**, 377; Shutalev, A.D.; Pagaev, M.T.; Ignatova, L.A. *ibid*, **1994**, 1093; Shutalev, A.D.; Komarova, E.N.; Pagaev, M.T.; Ignatova, L.A. *ibid*, **1993**, 1259; Shutalev, A.D.; Ignatova, L.A. *ibid*, **1991**, 228; Ignatova, L.A.; Shutalev, A.D.; Pagaev, M.T.; Unkovskii, B.V. *ibid*, **1988**, 234.

5. Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Intern.* **1985**, *17*, 317.

6. Shutalev, A.D. *Khim. Geterotsikl. Soedin.* (Rus), **1993**, 1389; Shutalev, A.D.; Komarova, E.N.; Pagaev, M.T.; Ignatova, L.A. *ibid*, **1993**, 1259; Shutalev, A.D.; Ignatova, L.A. *ibid*, **1991**, 228; Shutalev, A.D.; Ignatova, L.A.; Unkovskii, B.V. *ibid*, **1990**, 133.
