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A New Approach to the Synthesis of Hydrogenated Pyrimidine-2-imines

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Abstract: A new convenient method for the synthesis of hydrogenated 2-cyaniminopyrimidines has been developed. This method is based on preparation of a-tosyl substituted N-cyanoguanidines **11** followed by reaction with enolates of a-functionally substituted ketones to give 5-functionalized 2-cyanimino-4-hydroxypyrimidines **12**, **13**, **15**, **16**. All the obtained hydroxypyrimidines are readily converted into the corresponding 5-functionalized 2-cyanimino-1,2,3,4-tetrahydrohydropyrimidines **17-20** by heating in the presence of acids. Treatment of 5-acetyl-4-hydroxypyrimidines **12** with aq. KOH gives 4-hydroxypyrimidines **21** in result of removing the acetyl group.

Keywords: N-cyanoguanidine, N-cyano-N'-(1-tosyl-1-alkyl)guanidines, a-functionally substituted ketones, 2-cyanimino-4-hydroxyhexahydropyrimidines, 2-cyanimino-1,2,3,4-tetrahydropyrimidines.

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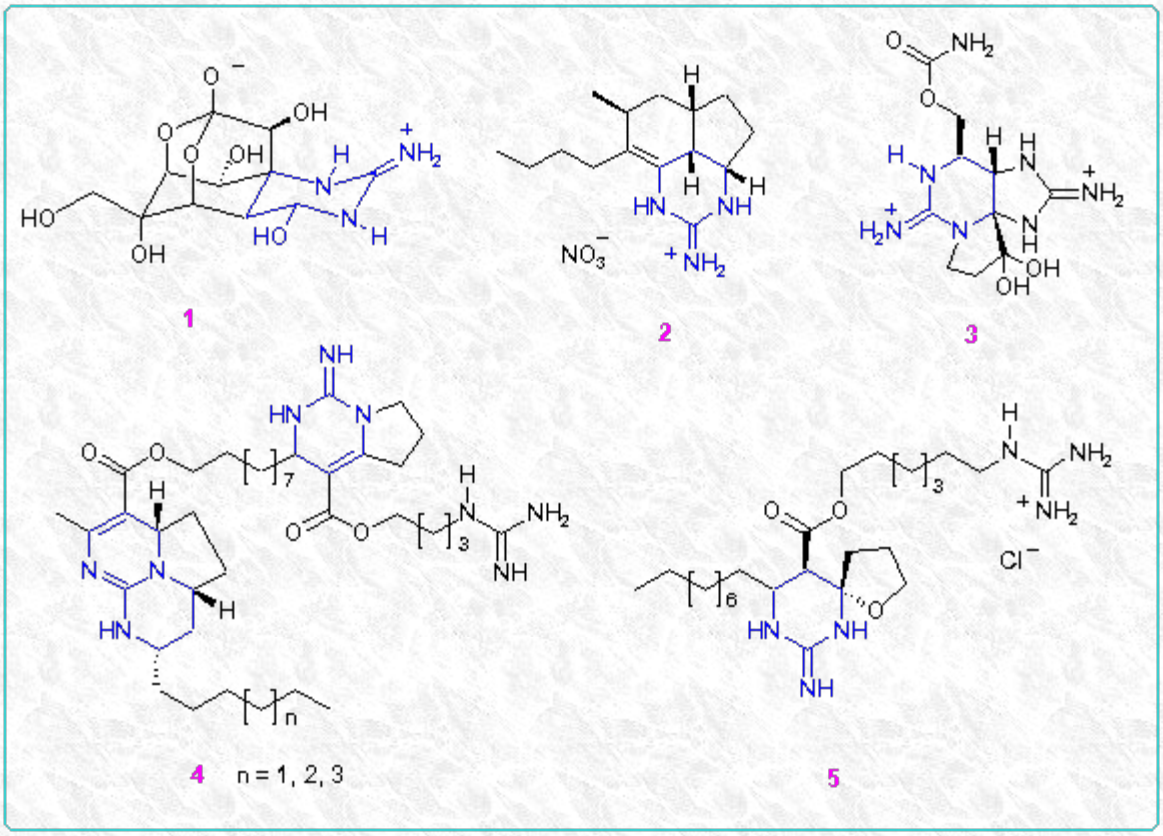
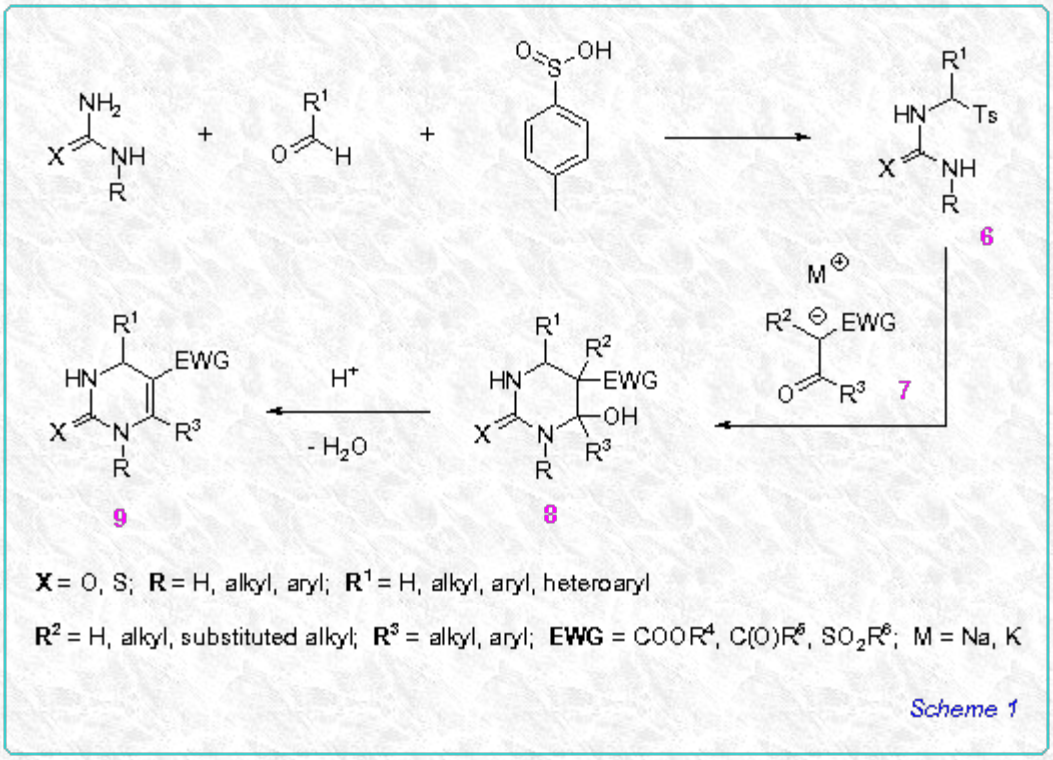
Introduction

Last years a large variety of compounds bearing a guanidine function with very interesting biological activities was isolated from natural products. The isolation and structure determination, synthesis, biosynthesis and the biological properties of such compounds were the subject of numerous reports (for reviews see [1-4]). Considerable attention has focused on natural and synthetic heterocycles containing a guanidine group. Many of these heterocyclic alkaloids were isolated from marine organisms. Typical representatives of these alkaloids are tetrodotoxin **1**, ptilocaulin **2**, saxitoxin **3**, batzelladine B **4**, crambescin B **5** and many others. All these alkaloids have a hydrogenated pyrimidine ring with 2-imino (or 2-amino) group.



The abundance of heterocyclic guanidine natural alkaloids which exhibit a broad range of biological properties has stimulated the development of various methods for their synthesis as well as synthesis of their analogs [1-4]. However, these methods suffer from their low universality. Really, they give possibility to synthesize only discrete compounds, and no series of related compounds for biological testings. Thus, the need for the development of new and general methods for heterocyclic guanidines synthesis, particularly hydrogenated pyrimidine-2-imines is of considerable importance.

Recently we have developed a convenient general method for the synthesis of 5-functionally substituted 4-hydroxyhexahydro- **8** and 1,2,3,4-tetrahydropyrimidine-2-thiones/ones **9** [5]. Principal step of this method is based on reaction of readily available a-tosyl substituted ureas or thioureas **6** with enolates of a-functionally substituted ketones **7** (*Scheme 1*).

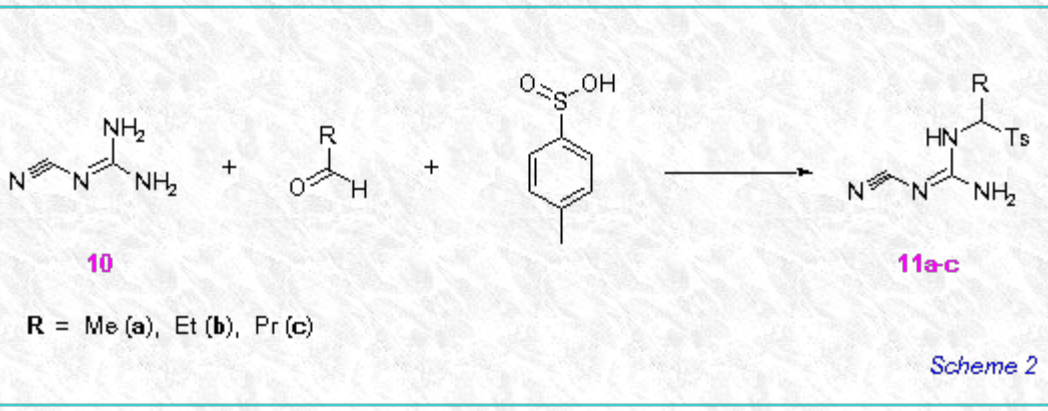


Scheme 1

We showed that the method is very flexible and offers access to a large variety of pyrimidines. We proposed that this approach could be applied to the synthesis of hydrogenated pyrimidine-2-imines. Thus, a-tosyl substututed guanidines were required for this synthesis. However, they could not be prepared by direct three-component condensation of guanidine, aldehydes and *p*-toluenesulfinic acid because of high basicity of guanidine. That is why instead of guanidine we decided to use guanidines bearing an electron-withdrawing group at nitrogen. We had in mind also that this group should be removed in one of subsequent stages of the synthesis. Thus, at the first time we used commercially available N-cyanoguanidine **10** (dicyandiamide) as starting compound. Here, we report the application of this approach to the preparation of 5-functionally substituted 2-cyanimino-4-hydroxyhexahydropyrimidines and 2-cyanimino-1,2,3,4-tetrahydropyrimidines.

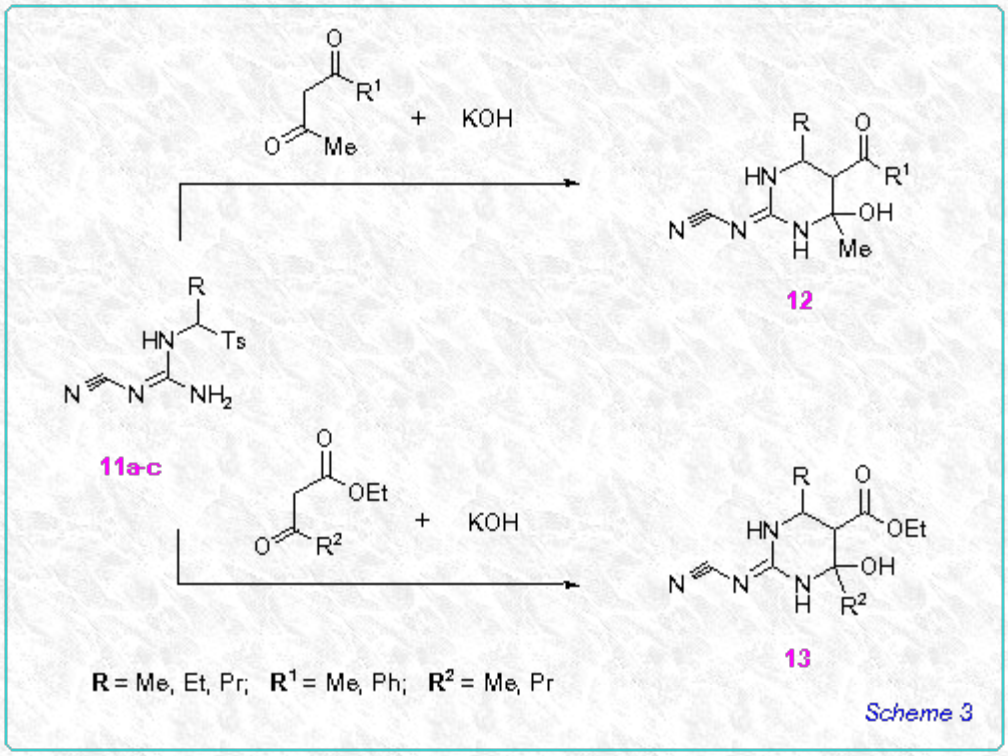
Results and Discussion

The desired a-tosyl substituted N-cyanoguanidines **11** were prepared by reaction of N-cyanoguanidine **10** with aliphatic aldehydes (acetaldehyde, propionic aldehyde and butyraldehyde) and *p*-toluesulfinic acid (water, r.t., 2-4 days) (*Scheme 2*). The products **11a-c** were isolated in 63-94 % yields by filtration of the reaction mixtures. It should be noted that the reaction involves only one of two unsubstituted nitrogen atoms of **10**. The obtained tosylguanidines **11a-c** owing to their good purity were used for the pyrimidine synthesis without further purification.

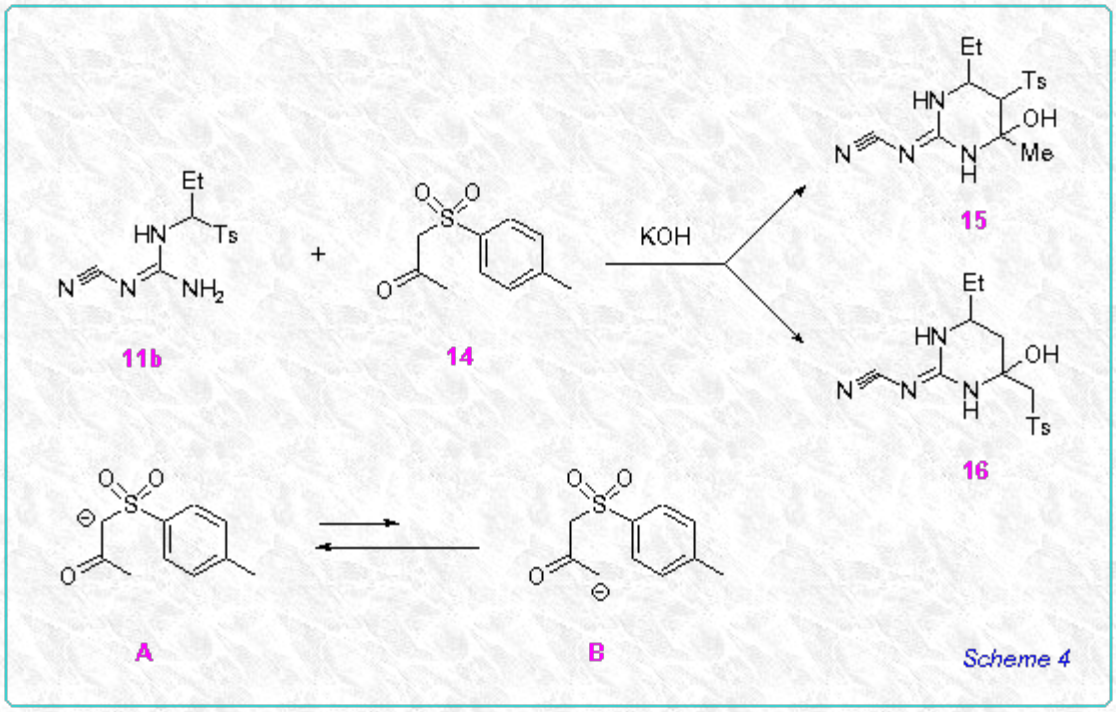


Scheme 2

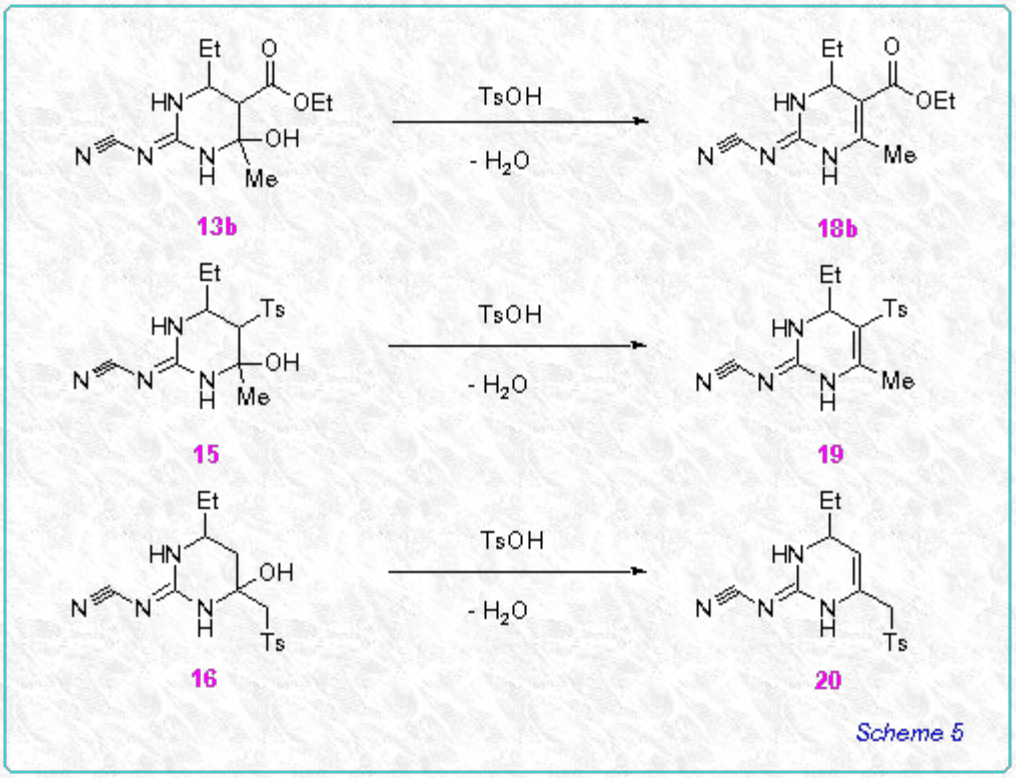
We found that **11a-c** reacted readily (r.t., 6-7 h) with potassium enolates of 1,3-dicarbonyl compounds (acetylacetone and benzoylacetone) generated *in situ* by treatment of the corresponding CH-acids with KOH in ethanol to give the corresponding 5-acyl-2-cyanimino-4-hydroxyhexahydropyrimidines **12** in 72-91 % yields. Analogously, ethyl 2-cyanimino-4-hydroxyhexahydropyrimidine-5-carboxylates **13** were prepared in 51-80 % yields starting from **11a-c** and b-oxoesters (ethyl acetoacetate and ethyl butyrylacetate) (*Scheme 3*). The pyrimidines **12**, **13** were formed in good diastereomeric purity.



Reaction of **11b** with potassium enolate of tosylacetone **14** (ethanol, r.t., 7.5 h) gave rather unusual result. Instead of **15** we obtained a mixture of **15** and **16** in the ratio of 3:1 (*Scheme 4*). Probably, formation of **16** can be explained by equilibrium of enolates **A** and **B**. Clearly, despite huge predominance of **A** over **B** in the equilibrium, reaction rate of **11b** with **B** is much higher than with **A** because of steric and electronic factors.

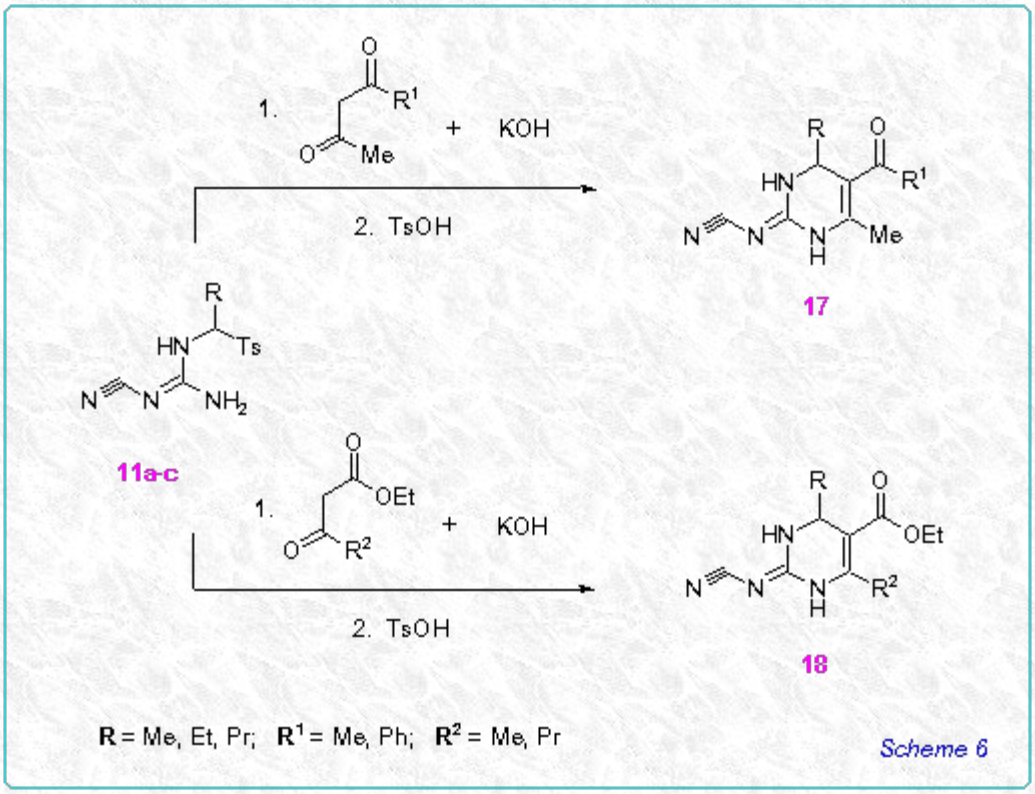


The obtained 2-cyanimino-4-hydroxypyrimidines **12**, **13**, **15**, **16** can be easily dehydrated in the presence of acids to produce the corresponding 2-cyanimino-1,2,3,4-tetrahydropyrimidines **17-20**. Really, refluxing **13b** and TsOH (0.2 equiv.) in ethanol for 1.2 h gave the tetrahydropyrimidine **18b** in 73 % yield. Analogously, a mixture of **19** and **20** in the ratio of 3:1 was prepared starting from the mixture of **15** and **16** (3:1) (*Scheme 5*). The pyrimidine **20** was easily separated by recryctallization from ethanol.



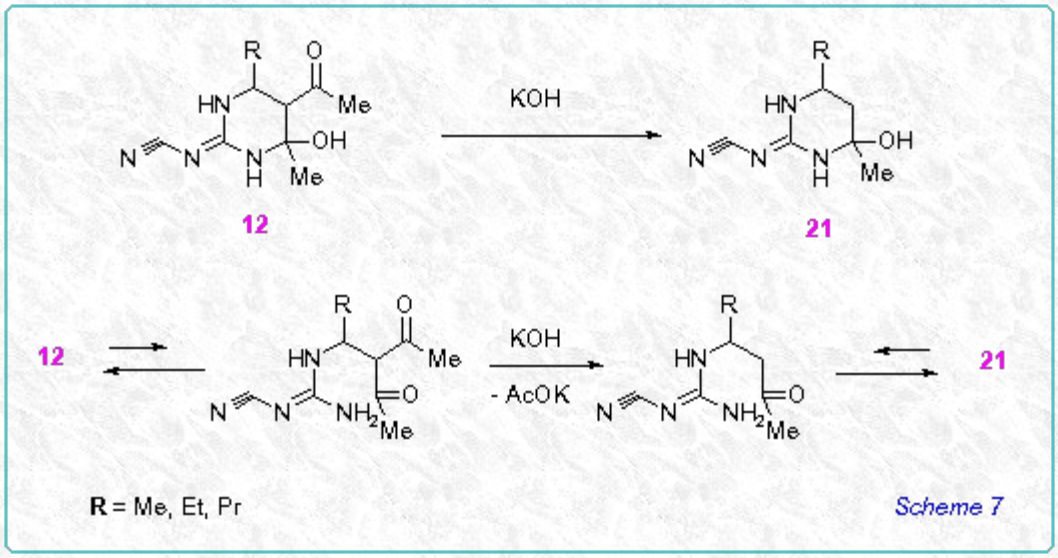
Mainly, however, 2-cyanimino-1,2,3,4-tetrahydropyrimidines **17**, **18** were synthesized by convenient one-pot procedure starting directly from a-tosyl substituted N-cyanoguanidines **11a-b**. According to this procedure, **11a-c** reacted (r.t., 6-7 h) with potassium enolates of 1,3-dicarbonyl compounds or b-oxoesters to afford **12**, **13** which without isolation were dehydrated after addition of TsOH (0.2 equiv.) to the reaction mixtures and subsequent

refluxing for 1-2 h to afford **17**, **18** in 46-73 % overall yields (*Scheme 6*).



Scheme 6

The prepared 2-cyaniminopyrimidines **12**, **13**, **15**-**20** can serve as starting compounds for syntheses of other 2-iminopyrimidines. For example, we found that 5-acetyl-4-hydroxypyrimidines **12** (R^1 = Me) in aq. KOH at r.t. give 4-hydroxypyrimidines **21** (27-82 % yields) in result of removing the acetyl group in **12** (*Scheme 7*). Probably, this transformation proceeds *via* the retro-Claisen reaction in the acyclic isomeric form of **12**.



Scheme 7

Conclusion

Thus, we have developed a new convenient method for the synthesis of hydrogenated 2-cyaniminopyrimidines using reaction of readily available a-tosyl substituted N-cyanoguanidines with enolates of 1,3-dicarbonyl compounds or b-

oxoesters. The obtained pyrimidines can serve as starting compounds in syntheses of a large number of multifunctional 2-iminopyrimidines. The application of the proposed method to the synthesis of other hydrogenated 2-iminopyrimidines, including heterocyclic guanidine natural alkaloids and their analogs, is currently in progress.

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