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**[A040]**

# Unexpected tosyl migration in acid catalyzed dehydration of 4-hydroxy-4-methyl-5-tosyl- 2-cyaniminohexahydropyrimidines

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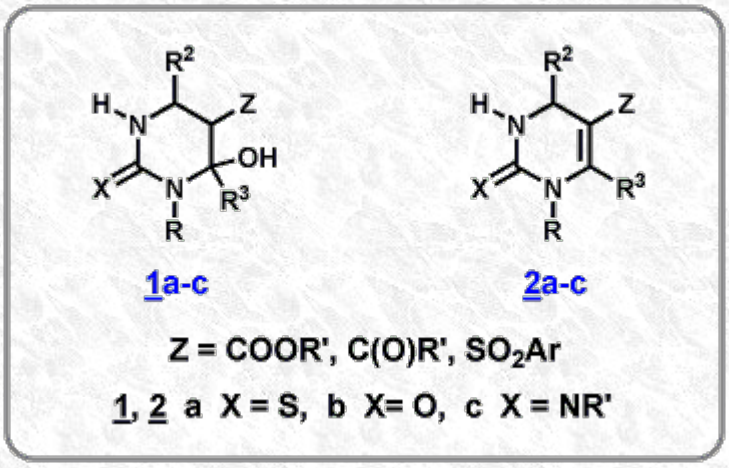
**Abstract:** Base-catalyzed dehydration of 2-cyanimino-4-hydroxy-4-methyl-5-tosylhexahydropyrimidines gives expected 2-cyanimino-5-tosyl-1,2,3,4-tetrahydropyrimidines. However, acid-catalyzed dehydration leads to mixture of the latter compounds and the products of tosyl group migration, namely 2-cyanimino-4-tosylmethyl-1,2,3,4-tetrahydropyrimidines. Plausible explanation of the obtained data is proposed.

**Keywords:** N-cyanoguanidine, N-cyano-N'-(1-tosyl-1-alkyl)guanidines, tosylacetone, 2-cyanimino-4-hydroxy-5-tosylhexahydropyrimidines, dehydration, 2-cyanimino-5-tosyl-1,2,3,4-tetrahydropyrimidines, 2-cyanimino-4-tosylmethyl-1,2,3,4-tetrahydropyrimidines, tosyl migration



## Introduction

Recently we have developed a new general approach to synthesis of 5-functionalized 4-hydroxyhexahydropyrimidine-2-thiones/ones **1a,b** and 1,2,3,4-tetrahydropyrimidine-2-thiones/ones **2a,b** bearing ester-, acyl- or arylsulfonyl group in the fifth position [1-4].



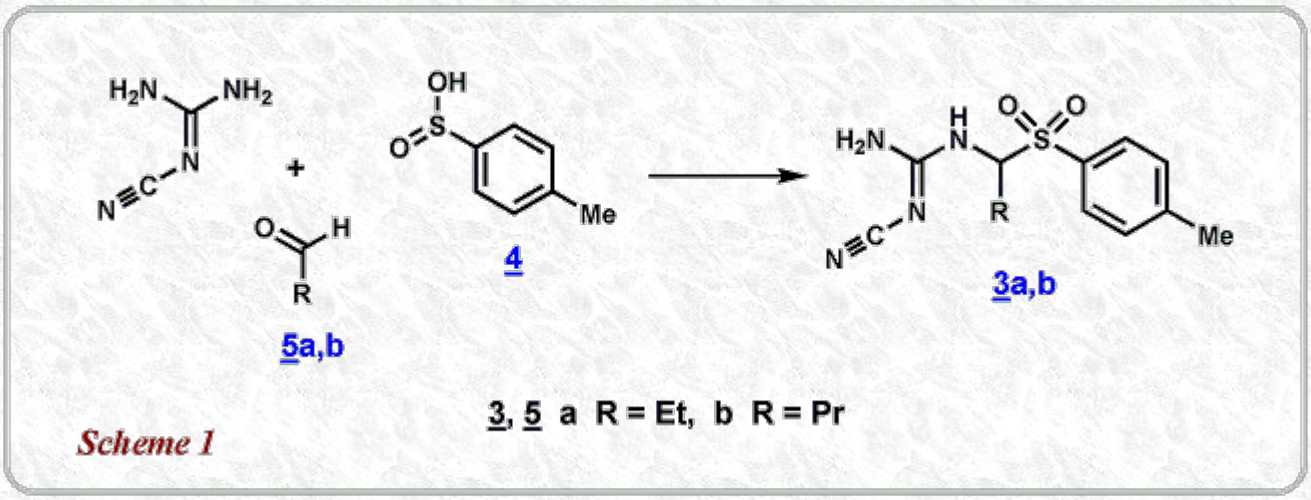

This approach is based on the reaction of readily available a-tosyl-substituted thioureas and ureas with enolates of b-oxoesters, 1,3-dicarbonyl compounds or a-arylsulfonylketones.

It seemed to us to be appropriate to apply the above-mentioned approach to the synthesis of 5-functionalized 4-hydroxyhexahydropyrimidin-2-imines **1c** and 1,2,3,4-tetrahydropyrimidin-2-imines **2c**. It is well known that some representatives of these compounds are the part of natural guanidine alkaloids (e.g., *tetrodotoxin*, *ptilocaulin*, *saxitoxin*, *batzelladine B*, *crambescin B*, etc.) which possess various biological activities [5].

In this communication we describe some preliminary results of 2-cyanimino-4-hydroxy-5-tosylhexahydropyrimidines and 2-cyanimino-5-tosyl-1,2,3,4-tetrahydropyrimidines synthesis.

## Results and Discussion

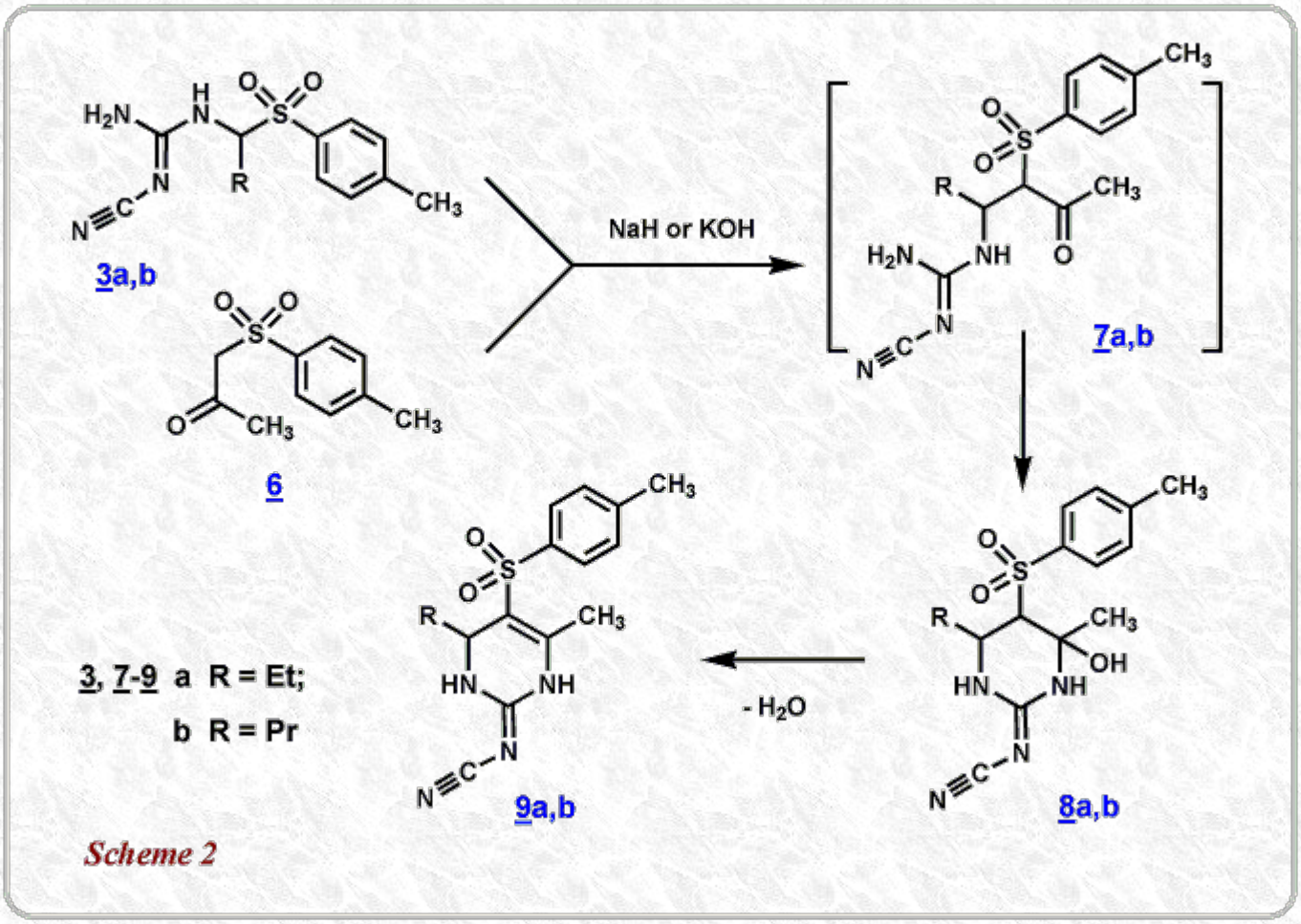
Starting a-tosyl-substituted cyanguanidines **3a,b** were obtained using three component condensation of cyanguanidine with aliphatic aldehydes (propanal **5a** and butanal **5b**) and *p*-toluenesulfinic acid **4** (*Scheme 1*).




This reaction proceeded in water at room temperature. However, the reaction time was found to be much longer (3-4 days) than in the case of thioureas and ureas [1-4]. Thus, we prepared **3a,b** in 92 and 94 % correspondingly.

We have shown that the obtained sulfones **3a,b** readily react with sodium or potassium enolates of tosylacetone **6** generated by treatment of the latter with sodium hydride in acetonitrile or potassium

hydroxide in ethanol to produce expected 4-hydroxy-5-tosylhexahydropyrimidine-2-imines **8a,b** (*Scheme 2*).




*Scheme 2*

It should be noted that some quantity of 5-tosyl-1,2,3,4-tetrahydropyrimidin-2-imines **9a,b** always forms in the described reaction along with hydroxypyrimidines **8a,b**. The amount of dehydration products **9a,b** depends on base (NaH or KOH) and reaction conditions (*Table 1*).

*Table 1*. Reaction of sulfones **3a,b** with tosylacetone **6** in the presence of bases

| Entry | Sulfone **3** | Reaction conditions | | | | Yield, %** | | **8**:**9** ratio* |
|---|---|---|---|---|---|---|---|---|
| | | Base | Solvent | Tempe-rature, oC | Time, h | **8** | **9** | |
| 1 | **3a** | NaH | MeCN | 20 | 7.5 | 71 | 11 | 69:31 |
| 2 | **3a** | KOH | EtOH | 20 | 24.3 | 20 | 70 | 22:78 |
| 3 | **3a** | KOH | EtOH | 20 | 47.5 | 3 | 75 | 4:96 |
| 4 | **3a** | KOH | EtOH | 20<br>78 | 8<br>1.5 | - | 40 | 0:100 |
| 5 | **3b** | NaH | MeCN | 20 | 4 | 62 | 21 | 75:25 |
| 6 | **3b** | NaH | MeCN | 20 | 6 | 36 | 44 | 69:31 |
| 7 | **3b** | KOH | EtOH | 20 | 47 | - | 82 | 0:100 |

* determined by $^1$H NMR spectroscopy; ** calculated using **8** : **9** ratios.

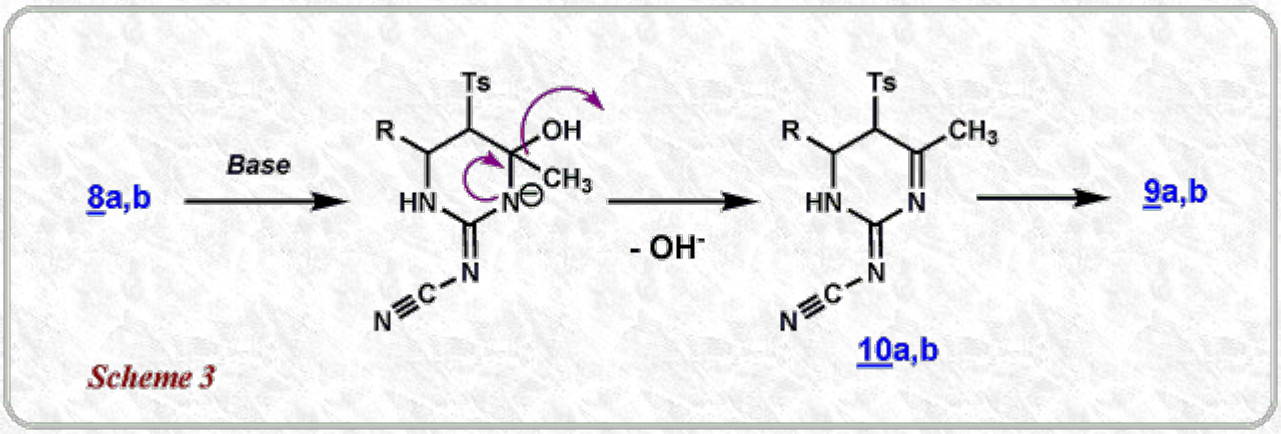
Amount of **9a,b** increases when KOH is used instead of NaH (*Table 1*, entry 1 *vs.* entry 2; entries 5, 6

*vs.* entry 7) and also with prolongation of time (entry 2 *vs.* entry 3; entry 5 *vs.* entry 6) and temperature rise (entry 1 *vs.* entry 4).

Thus, hexahydropyrimidin-2-imines **8a,**b with some amount of tetrahydropyrimidin-2-imines **9a,b** or pure **9a,b** can be obtained in the reaction of **3a,b** with **6** depending on reaction conditions.

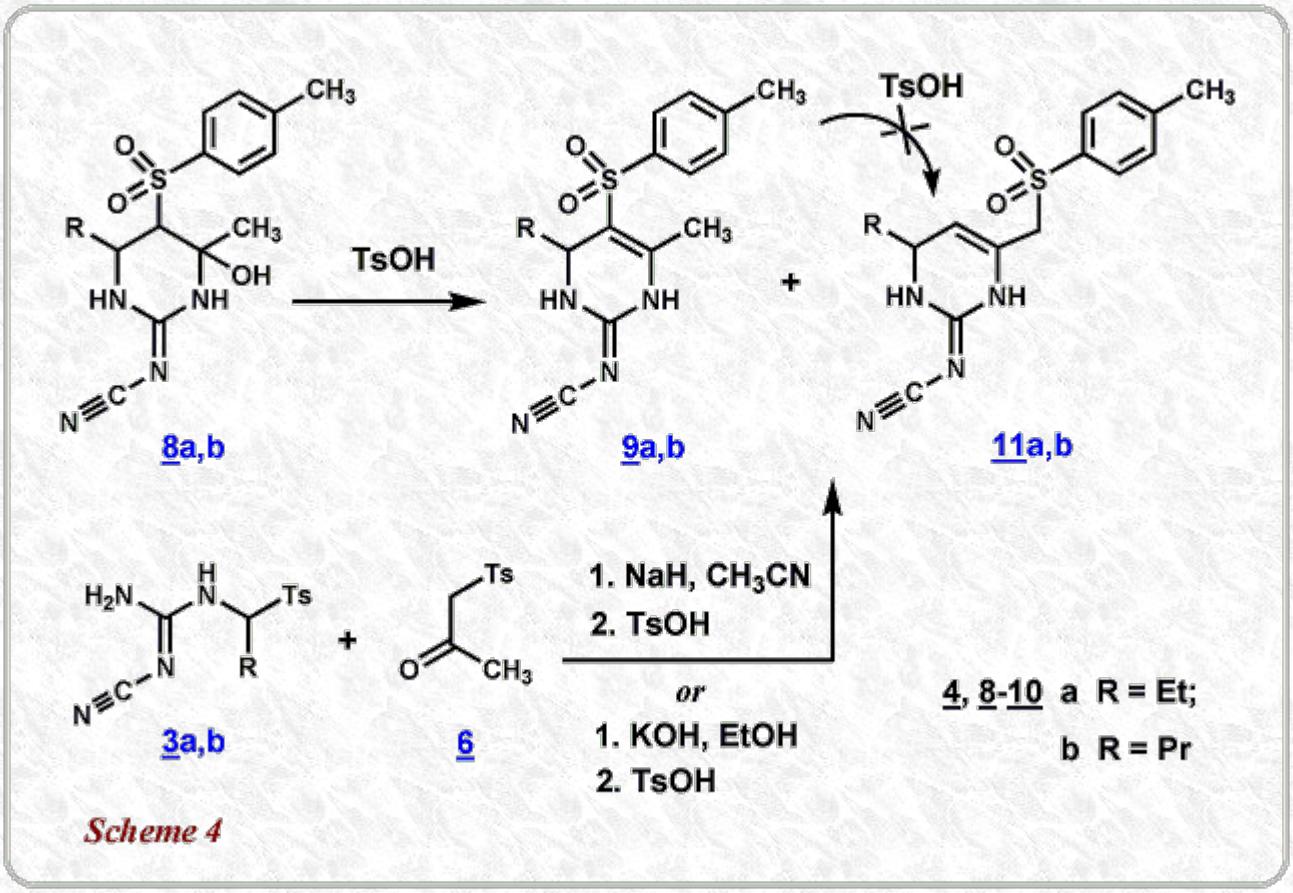
Formation of **9a,b** is rather unexpected in described above conditions. Actually, earlier we have demonstrated [1-4] that hydroxypyrimidines are the only products in reaction of a-tosyl-substituted (thio)ureas with b-oxoesters, 1,3-diketones or a-arylsulfonylketones in the presence of bases (NaH or KOH); the formation of dehydration products **2a,b** was not observed.

Tendency of hydroxypyrimidin-2-imines **8a,b** to dehydration can be explained by their high NH-acidity which facilitates dehydration through E1cB mechanism (*Scheme 3*). Initially formed pyrimidines **10a,**b turn into **9a,b** in result of imine-enamine tautomeric shift.



*Scheme 3*

The next stage of our work was investigation of acid-catalyzed dehydration of hydroxypyrimidines **8a,b**. We have found that reflux of **8a** in ethanol with 25 mol.% TsOH gives the expected pyrimidine **9a** along with considerable amount of its regioisomer **11a** *(Scheme 4*).




*Scheme 4*

Because the formation of **11a** was unexpected we investigated acid-catalyzed dehydration of hydroxypyrimidine **8a** in details (*Table 2*).

*Table 2.* Acid-catalyzed dehydration of hydroxypyrimidines **8a,b**

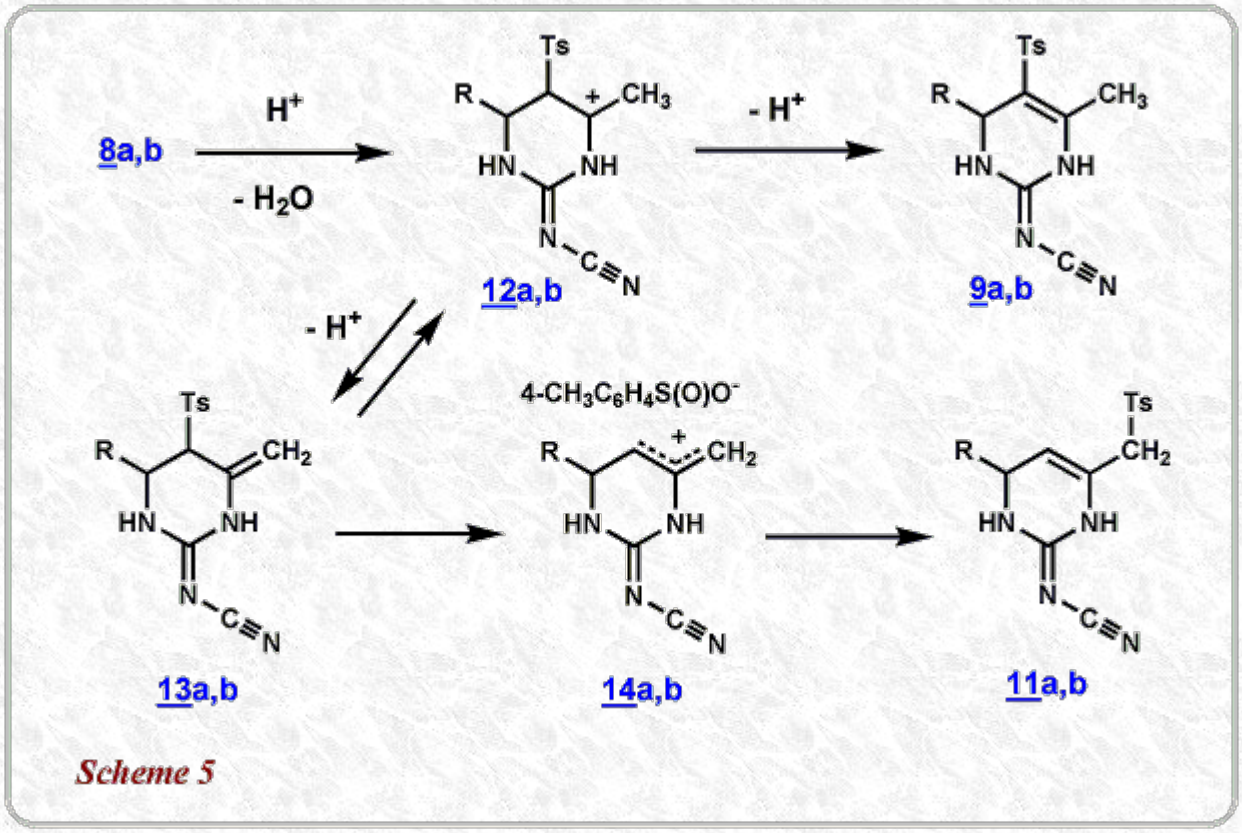
| Entry | Pyrimidine **8** | Reaction conditions | | Reaction product | Yield of **9**+**11**, % | **9**:**11** ratio* |
|---|---|---|---|---|---|---|
| | | Solvent | Catalyst | | | |
| 1 | **8a** | MeCN | TsOH | **9a**+**11a** | 95 | 52:48 |
| 2 | **8a** | EtOH | TsOH | **9a**+**11a** | 82 | 23:77 |
| 3 | **8a** | EtOH-$H_2O$ | TsOH | **9a**+**11a** | 81 | 30:70 |
| 4 | **8a** | EtOH | 4-$MeC_6H_4S(O)OH$ | **9a**+**11a** | 82 | 40:60 |
| 5 | **8b** | MeCN | TsOH | **9b**+**11b** | 100 | 63:37 |
| 6 | **8b** | EtOH | TsOH | **9b**+**11b** | 91 | 48:52 |

* Determined by $^1H$ NMR spectroscopy.

We have shown that yields of **11a** are considerably affected by solvent, especially by its change from aprotonic to protonic one. Thus, the amount of **11a** increases from 48 to 77 % with the replacement of acetonitrile by ethanol (entry 1 *vs.* entry 2). Further increasing of solvent solvation strength acts insignificantly (entry 2 *vs.* entry 3). Catalyst affects on the formation of **11a** too. Really, change of strong *p*-toluenesulfonic acid on weak *p*-toluenesulfinic acid leads to decreasing of the amount of **11**a from 77 to 60 % (entry 2 *vs.* entry 4).

The same principles were observed for dehydration of **8b** leading to mixture of **9b** and **11b** (entries 5, 6). It should be underlined that the formation of **11a,b** proceeds exactly from **8a,b** and not from **9a,b**. Indeed, reflux of **9a** in ethanol in the presence of TsOH (30 mol.%) did not lead to **11a**. Thus, we can

assume the following mechanism for the formation of **9a,b** and **11a,b** from **8a,b** (*Scheme 5*).




*Scheme 5*

The formation of **9a,b** from **8a,b** obviously proceeds through classic mechanism E1 *via* carbocations **12a,b**. Compounds **11a,b** also are formed *via* cations **12a,b** which then turn into 4-methylenpyrimidines **13a,b**. The allylic rearrangement of **13a,b** with tosyl group migration results in the formation of **11a,b**. Because of carbocation **14a,b** formation, the increasing of solvent solvation strength facilitates the rearrangement, as was proved experimentally (*Table 2*).

The supposed reaction way is consistent with the literature data about the higher stability of allylsulfones comparing with vinylsulfones [6]. The migration ability of arylsulfonyl groups in allylsulfones is also described in literature [7].

It should be noted that the observed tosyl migration in the course of dehydration of pyrimidin-2-imines **8a,b** was not found for 4-hydroxy-4-methyl-5-tosylhexahydropyrimidine-2-thiones/ones under the same conditions [8].

Compounds **9a** and **11a** can be obtained directly from cyanoguanidine **3a** without isolation of initially formed hydroxypyrimidine **8a** (*Scheme 4*). However, the amount of rearrangement product **11a** is within 9 %.

The obtained 4-tosylmethyltetrahydropyrimidines **11a,b** can be readily isolated from the mixtures with **9a,b** by means of single recrystallization from ethanol in high yields.

## Conclusion

Convenient method for the synthesis of earlier unknown 2-cyanimino-4-hydroxy-4-methyl-5-tosylhexahydropyrimidines has been developed. This method is based on preparation of a-tosyl-substituted N-cyanoguanidines followed by reaction with tosylacetone in the presence of bases. Base-catalyzed dehydration of the obtained hydroxyhexahydropyrimidines gives expected 2-cyanimino-5-

tosyl-1,2,3,4-tetrahydropyrimidines. However, acid-catalyzed dehydration leads to mixture of the latter compounds and the products of tosyl group migration, namely 2-cyanimino-4-tosylmethyl-1,2,3,4-tetrahydropyrimidines. Amount of migration products depends on solvent, catalyst and reaction conditions. Plausible explanation of the obtained data is proposed.

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