

An Unexpected Result of Base-Promoted Rearrangement of 4a-Acetyl-8a-hydroxydecahydroquinazoline-2-thione[†]

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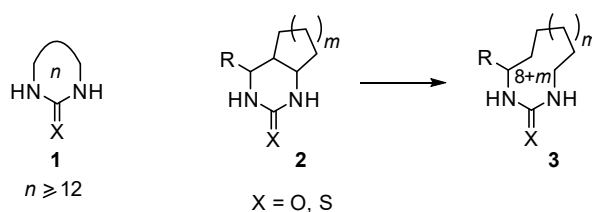
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Abstract: Treatment of 4a-acetyl-8a-hydroxydecahydroquinazoline-2-thione with NaH in acetonitrile leads to its isomerization into 1-hydroxy-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undecan-7-one followed by the C1-C6 bond cleavage to give *N*-acetyl-*N'*-(2-oxocyclohexyl)methylthiourea. The starting compound as a single diastereomer was prepared by the reaction between the K-enolate of 2-acetylcyclohexanone and *N*-(tosylmethyl)thiourea or *N*-(azidomethyl)thiourea.

Keywords: *N*-(azidomethyl)thiourea; *N*-(tosylmethyl)thiourea; 2-acetylcyclohexanone; 4a-acetyl-8a-hydroxydecahydroquinazoline-2-thione; rearrangement

1. Introduction

Macrocyclic ureas and thioureas are the objects of intensive research in modern organic chemistry [1–3]. We have recently become interested in the synthesis of macrocyclic ureas and thioureas **1** (Scheme 1), which until now have been practically unknown. We assumed that these heterocycles can be obtained using pyrimidine ring expansion by cleavage of the zero-bridge in 4,5-polymethylenehexahydropyrimidin-2-ones(thiones) **2**. Obviously, such cleavage will proceed especially smoothly if the carbon atoms forming this bridge contain a donor and acceptor substituent.



Scheme 1. Synthesis of macrocyclic ureas and thioureas **3** using pyrimidine ring expansion in 4,5-polymethylenehexahydropyrimidin-2-ones(thiones) **2**.

Previously, we developed a general convenient approach to 5-acyl-substituted 4-hydroxyhexahydropyrimidin-2-ones(thiones) **4** based on (thio)ureidoalkylation of enolates of 1,3-dicarbonyl compounds [4–7] (Scheme 2). The structural feature of pyrimidines **4** is the presence of an acceptor acyl group at the carbon C5 and a donor OH group at the carbon C4, which suggests a high tendency for the C4-C5 bond to break. Indeed, we found that, in the presence of a strong base (KOH, NaH, NaOH, etc.) in an aprotic solvent, these compounds undergo a rearrangement proceeding with the cleavage of the C4-C5 bond to give *N*-acyl-substituted *N'*-(γ -oxoalkyl)ureas and -thioureas [8,9] (Scheme 2).



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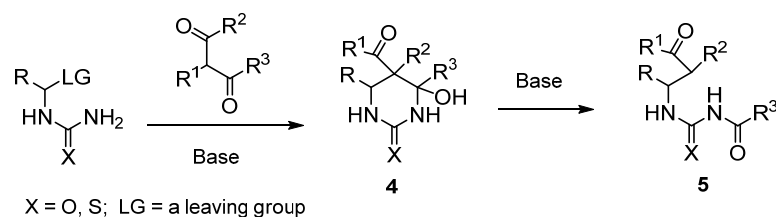
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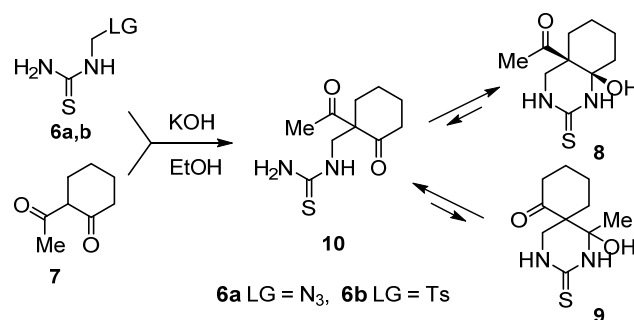
Scheme 2. Synthesis of 5-acyl-substituted 4-hydroxyhexahydropyrimidin-2-ones(thiones) **4** and base-promoted C4-C5 bond cleavage in **4** to give (thio)ureides **5**.

We suggested that such a rearrangement could be used in the synthesis of functionally substituted macrocyclic ureas and thioureas. Indeed, the formation of these compounds should have been expected during the rearrangement of bicyclic pyrimidines **5** with $R^2 + R^3 = (CH_2)_n$ or $R^1 + R^3 = (CH_2)_n$, etc.

Here, we report the reaction of *N*-(tosylmethyl)- and *N*-(azidomethyl)thiourea with 2-acetylcyclohexanone in the presence of KOH to afford the expected bicyclic 4a-acetyl-8a-hydroxydecahydroquinazolin-2-thione. We also describe a base-promoted cascade transformation of this compound to give *N*-acetyl-*N'*-[(2-oxocyclohexyl)methyl]-thiourea instead of the expected 10-membered cyclic thioureide.

2. Results and Discussion

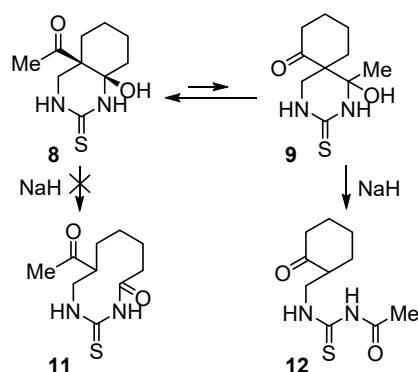
Readily available (azidomethyl)thiourea (**6a**) and (tosylmethyl)thiourea (**6b**) served as a starting thioureidomethylation reagents. We found that thiourea **6a** reacts smoothly with the K-enolate of 2-acetylcyclohexanone (EtOH, room temperature, 6.35 h) generated by the reaction of the corresponding CH-acid **7** with an equivalent amount of KOH to give a chromatographically pure product in 79% yield with the empirical formula of C₁₀H₁₆N₂O₂S. We also prepared the same compound in 72% yield by reacting thiourea **6b** with the K-enolate of 2-acetylcyclohexanone in EtOH. The structure of the obtained product established by 1D and 2D NMR spectroscopy corresponds to 4a-acetyl-8a-hydroxydecahydroquinazolin-2-thione (**8**) (Scheme 3). Another possible product of the above reaction, 1-hydroxy-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undecan-7-one (**9**), is not formed.



Scheme 3. Synthesis of 4a-acetyl-8a-hydroxydecahydroquinazolin-2-thione (**8**).

It should be noted that compound **8** is formed as a single diastereomer, structure of which was determined using ¹H, ¹H-NOESY. This diastereomer has (4a*R**, 8a*R**)-configuration and conformation with the axial orientation of the hydroxyl group and the equatorial orientation of the acetyl substituent.

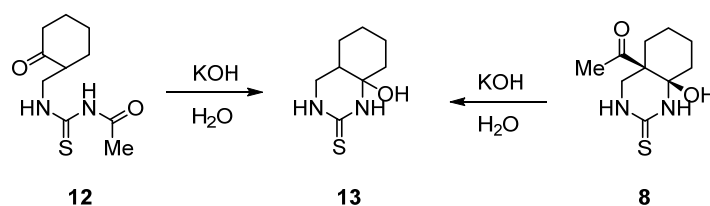
We expected that quinazolin-2-thione **8** in the presence of a strong base would give 10-membered cyclic thioureide **11** as a result of cleavage of the zero-bridge (Scheme 4). We found that treatment of compound **8** with NaH (1.5 equivalents) in dry MeCN at room temperature for 5 h 40 min resulted in a new substance, which was isolated from the reaction mixture in an 88% yield.



Scheme 4. Base-promoted cascade transformation of 4a-acetyl-8a-hydroxydecahydroquinazolin-2-thione (**8**) into *N*-acetyl-*N'*-[(2-oxocyclohexyl)methyl]thiourea (**12**).

However, to our surprise, the structure of the obtained product established by 1D and 2D NMR spectroscopy corresponded to *N*-acetyl-*N'*-[(2-oxocyclohexyl)methyl]-thiourea (**12**), and not the expected thioureaide **11** (Scheme 4).

An independent confirmation of the structure of the obtained product followed from the result of its alkaline hydrolysis (Scheme 5).



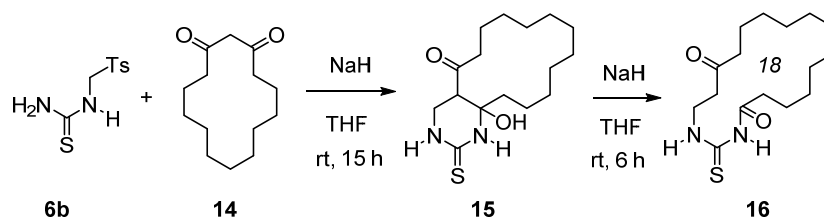
Scheme 5. Transformation of thioureaide **12** and quinazolin-2-thione **8** into compound **13** under the action of aqueous KOH.

Indeed, when thioureaide **12** was treated with aqueous KOH at room temperature, bicyclic hydroxypyrimidine **13** was obtained in 64% yield. The formation of this compound is explained by deacetylation of **12**, followed by cyclization of the resulting intermediate into **13**. The latter compound was also obtained from pyrimidine **8** under similar conditions (aqueous KOH, room temperature). This transformation apparently proceeds through the formation of the acyclic isomeric form **10**, followed by the removal of the acetyl group via Claisen retro-condensation, and further recyclization.

The transformation of quinazoline **8** into thioureaide **12** was also observed under other reaction conditions, but with lower yields. For example, treatment of **8** with 3 equivalents of NaH at room temperature gave compound **12** in a 56% yield. The reaction of **8** with NaH (1.51 equivalents) in dry tetrahydrofuran (THF) or with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (3 equivalents) in MeCN resulted in thioureaide **12** in 79% and 56% yield, respectively.

Thus, treatment of quinazolin-2-thione **8** with a strong base in an aprotic solvent leads to its rapid isomerization into 1-hydroxy-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undecan-7-one (**9**) followed by the C1-C6 bond cleavage to give the final compound **12**. Clearly, under strong basic conditions, the rate of this cascade transformation (**8**→**9**→**12**) is much higher than the rate of cleavage of the zero-bridge in **8** to give **11**. It can be explained by the dramatic effect of stereoelectronic factors associated with the relative configuration and conformation of compound **8** compared to compound **9**.

Since the preparation of 10-membered cyclic thioureaide **11** from quinazolin-2-thione **8** failed due to the rapid isomerization of **8** into **9** under basic conditions, we tested the methodology of macrocyclic (thio)ureas synthesis (see, Introduction) using a symmetric cyclic 1,3-diketone, cyclotetradecane-1,3-dione (**14**), for pyrimidine ring construction (Scheme 6).



Scheme 6. Synthesis of 18-membered cyclic thioureide **16**.

Thus, the reaction of sulfone **6b** with the Na-enolate of **14** in dry THF gave pyrimidine **15** in a 94% yield. Treatment of the latter with NaH (1.50 equivalents) in THF led to 18-membered cyclic thioureide **16** in a 36% isolated yield. Work is in progress to improve the yield of **16** and to synthesize other macrocyclic (thio)ureas.

3. Conclusions

In summary, we have shown that the reaction of *N*-(tosylmethyl)thiourea and *N*-(azidomethyl)thiourea with the K-enolate of 2-acetylcyclohexanone in EtOH proceeds exclusively regio- and stereoselectively to give (4a*R**,8a*R**)-4a-acetyl-8a-hydroxy-decahydroquinazoline-2-thione. Treatment of this compound with NaH in MeCN leads to its isomerization into 1-hydroxy-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undecan-7-one followed by the C1-C6 bond cleavage to form *N*-acetyl-*N'*-[(2-oxocyclohexyl)methyl]-thiourea. The expected cleavage of the zero-bridge to form 10-membered cyclic thioureide does not occur due to the effect of stereoelectronic factors. Synthesis of an 18-membered cyclic thioureide was carried out using (tosylmethyl)thiourea and cyclotetradecane-1,3-dione as starting materials.

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